

N-PYRAZINYL-PHENYLSULPHONAMIDES AND THEIR USE IN THE TREATMENT
OF CHEMOKINE MEDIATED DISEASES

The present invention relates to a sulphonamide compound, processes and intermediates
5 used in their preparation, pharmaceutical compositions containing them and their use in
therapy.

Certain sulphonamide compounds are known in the art, for example see
GB2295616, US patent 2002143024, WO 01/44239, EP 749964
10 and Esche, J; Wojahn, H. Arch. Pharm. (1966), 299(2), 147-153.

Chemokines play an important role in immune and inflammatory responses in various
diseases and disorders, including asthma and allergic diseases, as well as autoimmune
pathologies such as rheumatoid arthritis and atherosclerosis. These small-secreted
15 molecules are a growing superfamily of 8-14 kDa proteins characterised by a conserved
four cysteine motif. At the present time, the chemokine superfamily comprises three
groups exhibiting characteristic structural motifs, the Cys-X-Cys (C-X-C), Cys-Cys (C-C)
and Cys-X₃-Cys (C-X₃-C) families. The C-X-C and C-C families have sequence similarity
and are distinguished from one another on the basis of a single amino acid insertion
20 between the NH-proximal pair of cysteine residues. The C-X₃-C family is distinguished
from the other two families on the basis of having a triple amino acid insertion between the
NH-proximal pair of cysteine residues.

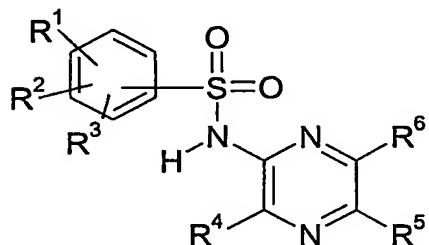
The C-X-C chemokines include several potent chemoattractants and activators of
25 neutrophils such as interleukin-8 (IL-8) and neutrophil-activating peptide 2 (NAP-2).

The C-C chemokines include potent chemoattractants of monocytes and lymphocytes but
not neutrophils. Examples include human monocyte chemotactic proteins 1-3 (MCP-1,
MCP-2 and MCP-3), RANTES (Regulated on Activation, Normal T Expressed and
30 Secreted), eotaxin and the macrophage inflammatory proteins 1 α and 1 β (MIP-1 α and
MIP-1 β), Thymus and Activation Regulated Chemokine (TARC, CCL17) and Macrophage
Derived Chemokine (MDC, CCL22).

The C-X₃-C chemokine (also known as fractalkine) is a potent chemoattractant and
35 activator of microglia in the central nervous system (CNS) as well as of monocytes, T
cells, NK cells and mast cells.

Studies have demonstrated that the actions of chemokines are mediated by subfamilies of G protein-coupled receptors, among which are the receptors designated CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10 and CCR11 (for the C-C family); CXCR1, CXCR2, CXCR3, CXCR4 and CXCR5 (for the C-X-C family) and CX₃CR1 for the C-X₃-C family. These receptors represent good targets for drug development since agents which modulate these receptors would be useful in the treatment of disorders and diseases such as those mentioned above.

10 The present invention therefore provides a compound of formula (I) and pharmaceutically acceptable salts, solvates or N-oxides thereof:



15 (I)

in which:

R¹, R² and R³ are independently hydrogen, halogen, cyano, CF₃, OCF₃, OC₁₋₆ alkyl or C₁₋₆ alkyl;

20 R⁴ is halogen, CO₂R¹²,

C₁₋₆ alkoxy where the alkyl group may form a 3-6 membered saturated ring or may be substituted with 1-3 fluorine atoms or a cyano group;

25 C₃₋₆ alkenyloxy or C₃₋₆ alkynyoxy where either may be optionally substituted with hydroxy or NR¹⁴R¹⁵;

OC₁₋₆ alkyl-X-C₁₋₆ alkyl where the alkyl groups may form a 3-6 membered saturated ring;

30 OC₁₋₆ alkylR¹¹, or OC₂₋₆ alkyl-X-R¹¹ where the alkyl group may form a 3-6 membered saturated ring and is optionally substituted with 1-3 groups selected from hydroxy, halogen, NR¹⁴R¹⁵, SR¹³, S(O)R¹³, S(O)R¹³ or COR¹³;

OC₁₋₆ alkylR¹⁶;

R⁵ and R⁶ are independently hydrogen, cyano, halogen, CO₂R¹², CONR¹⁴R¹⁵;

5 C₁₋₆ alkyl optionally substituted by hydroxy, NR¹⁴R¹⁵, or 1-3 fluorines;

C₁₋₆ alkylR¹¹ or XCH(R¹¹)C₁₋₆ alkyl or XCH(R¹⁶)C₁₋₆ alkyl where the alkyl group may be optionally substituted with 1-3 groups selected from hydroxy, and NR¹⁴R¹⁵;

10 NR¹⁴R¹⁵; N(R¹¹)R¹¹; X-(CH₂)qNR¹⁴R¹⁵; (CH₂)nNR¹⁴R¹⁵; NHC(O)C₁₋₆ alkyl optionally substituted by one or more hydroxy groups,

15 C₃₋₆ alkynyl or C₃₋₆ alkenyl optionally branched and optionally substituted with 1-3 groups selected from hydroxy, cyano, halogen and =O;

R¹¹; X-R¹²; X-C₁₋₆alkylR¹⁶; X-R¹⁶; X-(CH₂)nCO₂R¹²; X-(CH₂)nCONR¹⁴R¹⁵;
X-(CH₂)nR¹¹; X-(CH₂)nCN; X-(CH₂)qOR¹²; (CH₂)nOR¹²;
(CH₂)n-X-R¹¹; X-(CH₂)qNHC(O)NHR¹²; X-(CH₂)qNHC(O)R¹²;

20 X-(CH₂)qNHS(O)₂R¹²; X-(CH₂)qNHS(O)₂R¹¹; X-C₃₋₆alkenyl; X-C₃₋₆alkynyl;

n is 1, 2, 3, 4 or 5;

q is 2, 3, 4, 5 or 6;

25 X is NR¹³, O, S, S(O), S(O)₂;

R¹¹ is an aryl group or a 5-7 membered heteraromatic ring containing 1-4 heteroatoms selected from nitrogen, oxygen or sulphur each of which can be optionally substituted by 30 1-3 groups selected from halogen, C(O)NR¹⁴R¹⁵, C(O)OR¹², hydroxy, =O, =S, CN, NO₂, COR¹³, NR¹⁴R¹⁵, X(CH₂)qNR¹⁴R¹⁵, (CH₂)nNR¹⁴R¹⁵, (CH₂)nOH, SR¹³, S(O)R¹³, S(O)₂R¹³ C₁₋₆ alkyl-X-C₁₋₆ alkyl, C₁₋₆ alkyl or C₁₋₆ alkoxy where the alkyl group may form a 3-6 membered ring or is optionally substituted with 1-3 groups selected from hydroxy, halogen, NR¹⁴R¹⁵, SR¹³, S(O)R¹³, S(O)₂R¹³;

R¹² and R¹³ are independently hydrogen or C₁₋₆ alkyl where the alkyl group may be substituted with 1-3 fluorine atoms or may form a saturated 3-6 membered ring;

R¹⁴ and R¹⁵ are independently hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl or (CH₂)_qOH,

or R¹⁴ and R¹⁵ together with the nitrogen atom to which they are attached form a 4-8 membered saturated ring containing 1-3 heteroatoms selected from nitrogen, oxygen and sulphur and optionally substituted by C₁₋₆ alkyl, C₁₋₆ alkyl-OH, or hydroxy; and

R¹⁶ is a 4-8 membered saturated ring containing 1-3 heteroatoms selected from nitrogen, oxygen or sulphur and optionally substituted with 1-3 groups selected from hydroxy, cyano, halogen and =O,

provided that:

- when R⁴ is halogen or C₁₋₄alkoxy and R⁵ is hydrogen, halogen, C₁₋₄alkyl, C₁₋₂alkoxy, C₁₋₂alkylthio, trifluoromethyl or ethynyl and when one of R¹, R² or R³ is C₁₋₆alkyl or C₁₋₆alkoxy and is meta to the sulphonamide group then the group ortho to both the sulphonamide group and the C₁₋₆alkyl or C₁₋₆alkoxy group is not hydrogen,
- when R⁴ is halogen or C₁₋₄alkoxy and R⁵ is hydrogen, halogen, C₁₋₄alkyl, C₁₋₂alkoxy, C₁₋₂alkylthio, trifluoromethyl or ethynyl and when one of R¹, R² or R³ is C₁₋₆alkyl or C₁₋₆alkoxy and is ortho to the sulphonamide group then the group ortho to the C₁₋₆alkyl or C₁₋₆alkoxy and also meta to the sulphonamide group is not hydrogen,
- when two of R¹, R², R³ are hydrogen and the other is a methyl group para to the sulphonamide and R⁴ is methoxy then R⁵ is not hydrogen or bromo, and
- when R⁵ is methyl and R⁶ is methoxy and one of R¹, R² or R³ is bromo or iodo and the other two are both hydrogen, then the bromo or iodo group is not ortho to the sulphonamide group.

The term aryl includes phenyl and naphthyl. The term alkyl, whether alone or as part of another group, includes straight chain and branched chain alkyl groups. Examples of 5- to 7-membered heteroaromatic ring containing 1 to 4 heteroatoms include thienyl, furanyl, pyrrolyl, imidazolyl, pyridyl, pyrazinyl, pyrimidyl, pyridazinyl, triazinyl, oxazolyl, thiazolyl, isoxazolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, triazolyl and tetrazolyl. Examples of saturated 4- to 8-membered rings containing 1 to 3 heteroatoms include

morpholine, piperidine and azetidine. Substituents on any rings can be present in any suitable ring position including suitable substituents on nitrogen atoms.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (I) and mixtures thereof including racemates. Tautomers and mixtures thereof also form an aspect of the present invention.

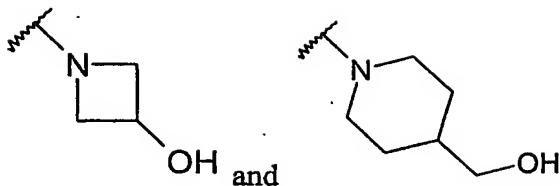
Preferred halogen groups for R^1 , R^2 and R^3 are chloro, bromo and fluoro. Preferably one of R^1 , R^2 and R^3 is hydrogen and the other is chloro, bromo or methyl. More preferably R^1 and R^2 are chloro at the 2- and 3-positions of the phenyl ring and R^3 is hydrogen (i.e. 2,3-dichlorophenyl), R^1 and R^3 are chloro at the 2- and 4-positions of the phenyl ring and R^2 is hydrogen (i.e. 2,4-dichlorophenyl) or R^1 is chloro at the 2-position and R^2 is methyl at the 3-position of the phenyl ring and R^3 is hydrogen (i.e 2-chloro-3-methylphenyl). Most preferably R^1 and R^2 are chloro at the 2- and 3-positions of the phenyl ring and R^3 is hydrogen (i.e. 2,3-dichlorophenyl).

In a further aspect the invention provides a compound of formula (I) as defined above but without the provisos where R^1 and R^2 are chloro at the 2- and 3-positions of the phenyl ring and R^3 is hydrogen (i.e. 2,3-dichlorophenyl), R^1 and R^3 are chloro at the 2- and 4-positions of the phenyl ring and R^2 is hydrogen (i.e. 2,4-dichlorophenyl) or R^1 is chloro at the 2-position and R^2 is methyl at the 3-position of the phenyl ring and R^3 is hydrogen (i.e 2-chloro-3-methylphenyl).

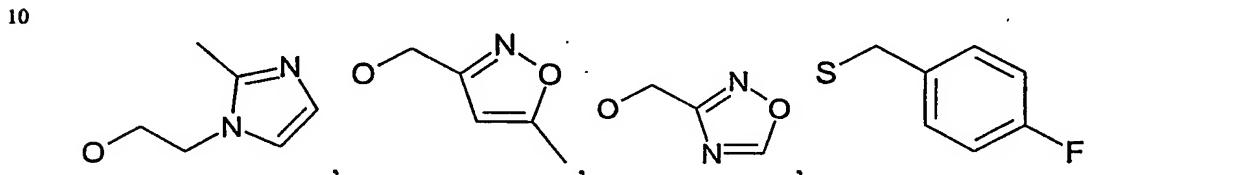
For the group R^4 examples of C_{3-6} alkenyloxy include $OCH_2CH=CH_2$, examples of C_{3-6} alkynyloxy include OCH_2CCH , examples of OC_{1-6} alkyl-O- C_{1-6} alkyl include OCH_2CH_2OMe , examples of OC_{1-6} alkyl R^{11} include OCH_2R^{11} , and examples of OC_{1-6} alkyl R^{16} include $OCH_2pyrrolidine$.

Preferred groups for R^4 include C_{1-6} alkoxy such as methoxy, 2-furanylmethoxy, bromo, chloro, 2-methoxyethoxy, (5-methyl-3-isoxazolyl)methoxy, 2-, 3- or 4-pyridylmethoxy, 3-pyridazinylmethoxy, methoxy, 2-(1-imidazolyl)ethoxy, (2-methyl-4-oxazolyl)methoxy and 4-methoxyphenylmethoxy. More preferably R^4 is methoxy.

For R^5 and R^6 examples of $NR^{14}R^{15}$ includes morpholine, pyrrolidine, NMe_2 , $NHCH_2CH_2OMe$, $NHMe$, and the groups below:



Examples of X-(CH₂)_qNR¹⁴R¹⁵ include SCH₂CH₂NH₂ and SCH₂CH₂NMe₂, examples of (CH₂)_nNR¹⁴R¹⁵ include CH₂morpholine, examples of X-R¹² includes SMe, OMe, OEt, OH, SO₂Me, examples of X-C₁₋₆alkylR¹⁶ includes OCH₂pyrrolidine, examples of X-(CH₂)_nCO₂R¹² includes SCH₂CO₂H, SCH₂CO₂Me, SCH₂CH₂CO₂Me, examples of X-(CH₂)_nCONR¹⁴R¹⁵ includes SCH₂CONH₂, SCH₂CONHMe, OCH₂CONEt₂, examples of X-(CH₂)_nR¹¹ includes the groups below:

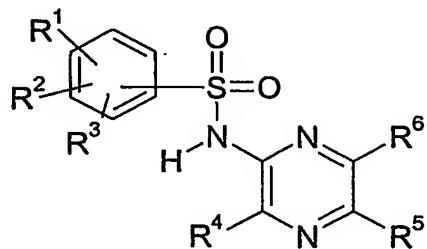


15 Examples of X-(CH₂)_nCN, includes SCH₂CN, examples of X-(CH₂)_qOR¹² includes OCH₂CH₂OMe, examples of (CH₂)_nOR¹² includes CH₂OH, CH₂OMe, examples of X-(CH₂)_qNHC(O)NHR¹² includes SCH₂CH₂NHC(O)NH₂, and examples of X-(CH₂)_qNHC(O)R¹² includes NHCH₂CH₂NHC(O)Me. Examples of NHC(O)C₁₋₆ alkyl optionally substituted by one or more hydroxy groups includes NHCOCH₂OH.

20 Preferred groups for R⁵ include hydrogen, halogen such as bromo and chloro, phenyl, C₁₋₆ alkyl such as methyl, CH₂OH, cyano and 2-aminothiophenol. More preferably R⁵ is hydrogen, methyl, CH₂OH or halogen such bromo or chloro.

25 Preferred groups for R⁶ include hydrogen, C₁₋₆ alkyl, CH₂OH and halogen, more preferably hydrogen, methyl, CH₂OH or chloro.

In a further aspect the invention provides a compound of formula (IA):



(IA)

in which

5 R¹, R² and R³ are independently hydrogen, halogen, cyano, CF₃, OCF₃, C₁₋₆ alkenyl or C₁₋₆ alkyl;

R⁴ is halogen, C₁₋₆ alkoxy or OR⁹;

10 R⁵ and R⁶ are independently hydrogen, halogen, C₁₋₆ alkoxy, C₁₋₆ alkylthio, cyano, R⁹, OR⁹, NR⁹R¹⁰, SR⁹, S(CH₂)_nCO₂H, S(CH₂)_nCO₂R¹², S(CH₂)_nCONR¹²R¹³, S(CH₂)_nR¹¹ or a 5- to 7-membered heteroaromatic or saturated ring containing 1 to 3 heteroatoms selected from nitrogen, oxygen and sulphur;

15 n is 1, 2 or 3;

R⁹ and R¹⁰ are independently hydrogen, C₁₋₆ alkyl optionally substituted by hydroxy, C₁₋₆ alkoxy or NHCOC₁₋₆ alkyl, or R⁹ and R¹⁰ are optionally substituted aryl, C₁₋₆ alkyl-aryl or C₁₋₆ alkyl-R¹¹ or R⁹ and R¹⁰ together with the nitrogen atom to which they are attached form a 4- to 8-membered saturated ring containing 1 to 3 heteroatoms selected from nitrogen, oxygen and sulphur and optionally substituted by C₁₋₆ alkyl or C₁₋₆ alkyl-OH; and

20 R¹¹ is a 5- to 7-membered heteraromatic ring containing 1 to 3 heteroatoms selected from nitrogen, oxygen and sulphur and optionally substituted by C₁₋₆ alkyl; and R¹² and R¹³ are independently hydrogen or C₁₋₆ alkyl.

For compounds (IA) R¹, R² and R³ are independently hydrogen, halogen, cyano, CF₃, OCF₃, C₁₋₆ alkenyl or C₁₋₆ alkyl, preferred halogen groups being chloro. Preferably one of R¹, R² and R³ is methyl, ethenyl, cyano, chloro, fluoro, iodo or two are chloro or all three are fluoro. More preferred are compounds where R¹ – R³ together with the phenyl group to which they are attached form a 3-chloro-2-methylphenyl or a 2,3-dichlorophenyl group.

For compounds (IA) preferred groups for R⁴ include halogen such as bromo and chloro, C₁₋₆ alkoxy such as methoxy and ethoxy, C₁₋₆ alkyl or OR⁹ where R⁹ is CH₂R¹¹ where R¹¹ is a 5- or 6-membered heteraromatic ring containing 1 or 2 heteroatoms.

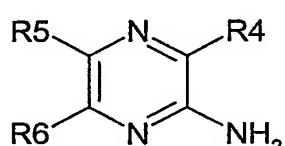
More preferably R⁴ is methoxy, halogen, such as chloro, or OR⁹ where R⁹ is CH₂R¹¹ where R¹¹ is furanyl, 5-methyl-3-isoxazolyl, pyridyl optionally substituted by methyl, pyridazinyl, pyrazinyl, 1-methyl-6-oxo-1,6-dihydro-3-pyridinyl.

5 For compounds (IA) preferably R⁵ is hydrogen, methyl, bromo, chloro, methoxy, morpholinyl, pyrrolinyl, dimethylamino, hydroxy, 2-methoxyethoxy, pyrazinyl, pyrimidinyl, O-Ph-CO₂H, 2-hydroxyethylamino, 2-methoxyethylamino, NHCH₂CH₂NHCOMe, cyano, 4-hydroxymethyl-1-piperidinyl, SMe, NHMe, or 2,4-difluorophenyl.

10 For compounds (IA) preferably R⁶ is hydrogen or chloro.

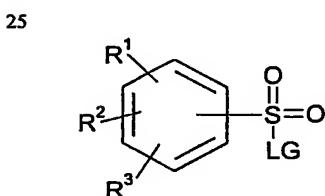
Preferred compounds of formula (I)/(IA) include those exemplified herein both in free base form and as pharmaceutically acceptable salts.

15 According to the invention there is also provided a process for the preparation of compound (I) which comprises reaction of a compound of formula (II):



20 (II)

where R⁴, R⁵ and R⁶ are as defined in formula (I) or are protected derivatives thereof with a compound of formula (III):



25 (III)

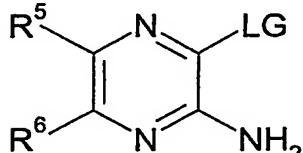
where R¹, R² and R³ are as defined in formula (I) or are protected derivatives thereof and
30 LG is a leaving group,
and optionally thereafter

- removing any protecting groups,
- forming a pharmaceutically acceptable salt.

Preferred leaving groups LG include halogen such as chloro. Preferably the reaction between compounds (II) and (III) is carried out by treating compound (II) with a base such as sodium hydride or potassium tert-butoxide in a suitable solvent such as 1,2-dimethoxyethane or tetrahydrofuran.

Where R⁴ is C₁₋₆ alkoxy where the alkyl group may form a 3-6 membered saturated ring or may be substituted with 1-3 fluorine atoms or a cyano group; C₃₋₆ alkenyloxy or C₃₋₆ alkynyoxy where either may be optionally substituted with hydroxy or NR¹⁴R¹⁵; OC₁₋₆ alkyl-X-C₁₋₆ alkyl where the alkyl groups may form a 3-6 membered saturated ring; OC₁₋₆ alkylR¹¹, or OC₂₋₆ alkyl-X-R¹¹ where the alkyl group may form a 3-6 membered saturated ring and is optionally substituted with 1-3 groups selected from hydroxy, halogen, NR¹⁴R¹⁵, SR¹³, S(O)₂R¹³, S(O)R¹³; or OC₁₋₆ alkylR¹⁶; compounds of formula (II) can be prepared by treating a compound of the formula (IV), where LG is a leaving group (such as chlorine or bromine):

20



(IV)

25



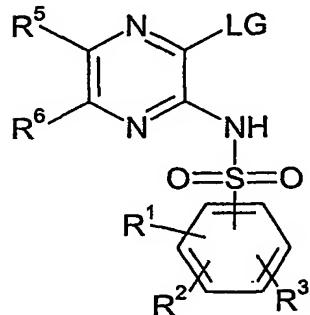
(V)

in a suitable solvent (such as 1,2-dimethoxyethane, N,N-dimethylformamide or tetrahydrofuran) with a suitable base such as sodium hydride or potassium tert-butoxide at a suitable temperature such as 25°C to 60°C.

Where R^4 is C_{1-6} alkoxy where the alkyl group may form a 3-6 membered saturated ring or may be substituted with 1-3 fluorine atoms or a cyano group;

C_{3-6} alkenyloxy or C_{3-6} alkynyoxy where either may be optionally substituted with hydroxy or $NR^{14}R^{15}$;

- 5 OC_{1-6} alkyl-X- C_{1-6} alkyl where the alkyl groups may form a 3-6 membered saturated ring; OC_{1-6} alkyl R^{11} , or OC_{2-6} alkyl-X- R^{11} where the alkyl group may form a 3-6 membered saturated ring and is optionally substituted with 1-3 groups selected from hydroxy, halogen, $NR^{14}R^{15}$, SR^{13} , $S(O)_2R^{13}$, $S(O)R^{13}$; or OC_{1-6} alkyl R^{16} ;
- 10 compounds of formula (I) can be prepared by treating a compound of the formula (VI), where LG is a leaving group (such as chlorine or bromine):



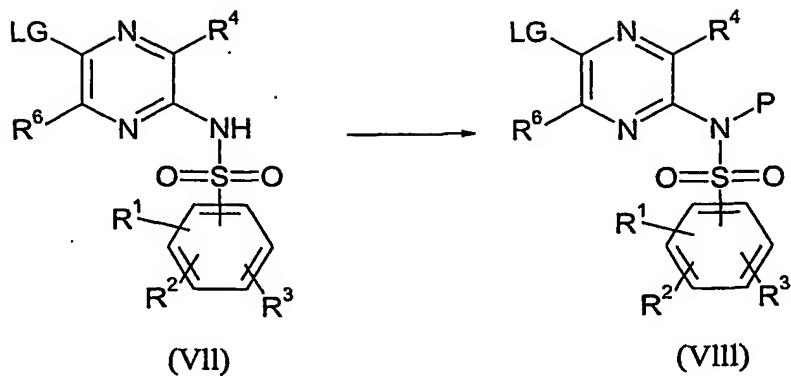
(VI)

15

with a compound of formula (V)

- in a suitable solvent (such as 1,2-dimethoxyethane, *N,N*-dimethylformamide or tetrahydrofuran) with a suitable base such as sodium hydride or potassium tert-butoxide
- 20 at a suitable temperature such as 25°C to 60°C.

- Compounds of structure (VIII) can be prepared by taking a compound of formula (VII) where LG is a leaving group (such as chlorine or bromine) and protecting the sulfonamide as for example the trimethylsilyethoxymethyl ether (SEM) or methoxymethyl ether (MOM) by the standard literature methods (such as SEM-chloride or MOM-chloride) in a suitable solvent (such as tetrahydrofuran) with a suitable base (such as triethylamine) at a suitable temperature (such as 0-20°C) to afford compound of the formula (VIII):
- 25



Compound of formula (VIII) could then be treated with compounds of formulae (IX):

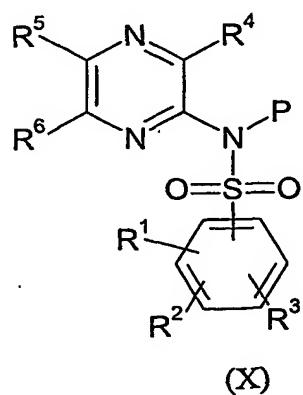
5

R⁵-H

(IX)

10 where R⁵-H is a primary or secondary amine, thiol or alcohol as defined above (i.e. where R⁵ is a group containing an X moiety where X is NR¹³, O or S), in a suitable solvent (such as tetrahydrofuran or acetonitrile) with or without a suitable base (such as sodium hydride, caesium carbonate or triethylamine) at a suitable temperature ranging from 25-85°C to afford compound of the formula (X):

15



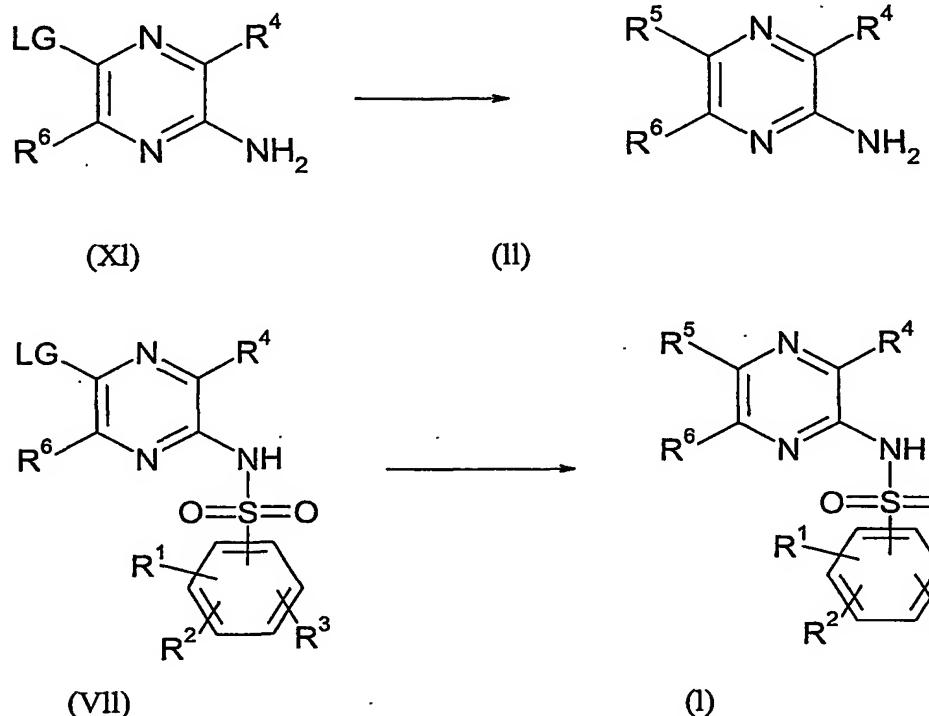
The protecting group (P) can then be removed by standard methods to afford compound of formula (I).

20

Compounds of structure (II) or (I), where R⁵ is an optionally substituted aryl or heteroaryl ring as defined in the claims, can be prepared by taking a compound of formula (XI) or (VII) where LG is a suitable leaving group such as bromine, chlorine or iodine and reacting

it with an aryl or heteroaryl boronic acid such as phenyl boronic acid, a palladium catalyst such as [1,1'-bis(diphenylphosphino)ferrocene]palladium (II) chloride, a suitable base such as caesium fluoride, sodium acetate or caesium carbonate and a suitable solvent such as methanol or ethanol and heating between 40-80°C

5



10

Compounds of formula (II) and (I) where R⁵ or R⁶ is CO₂R¹³ can be prepared by reacting a compound of formula (II) or (I), where R⁵ or R⁶ is bromine or iodine, in a suitable solvent such as R¹³OH or dioxane containing R¹³OH, a suitable tertiary amine such as triethylamine, a suitable palladium catalyst such as [1,1'-bis(diphenylphosphino)ferrocene]palladium (II) chloride under an atmosphere of carbon monoxide usually at 2-10 bar, ideally at 4-6 bar and at a temperature of 70-120 °C. Compounds of formula (II) and (I) where R⁵ or R⁶ is CONR¹⁴R¹⁵ can be prepared by reacting a compound of formula (II) or (I), where R⁵ or R⁶ is bromine or iodine, in a suitable solvent such as dioxane containing NHR¹⁴R¹⁵, a suitable tertiary amine such as triethylamine, a suitable palladium catalyst such as [1,1'-bis(diphenylphosphino)ferrocene]palladium (II) chloride under an atmosphere of carbon monoxide usually at 2-10 bar, ideally at 4-6 bar and at a temperature of 70-120 °C. Compounds of formula (I) where R⁵ or R⁶ is CH₂OH can be prepared from compounds of formula (I) where R⁵ or R⁶ is CO₂R¹³ by reduction using a suitable reducing agent such as

15

20

25

lithium triethylborohydride in a suitable solvent such as tetrahydrofuran at a temperature of 0-10°C.

Compounds of formula (I) where R⁵ or R⁶ is CHO can be prepared from compounds of

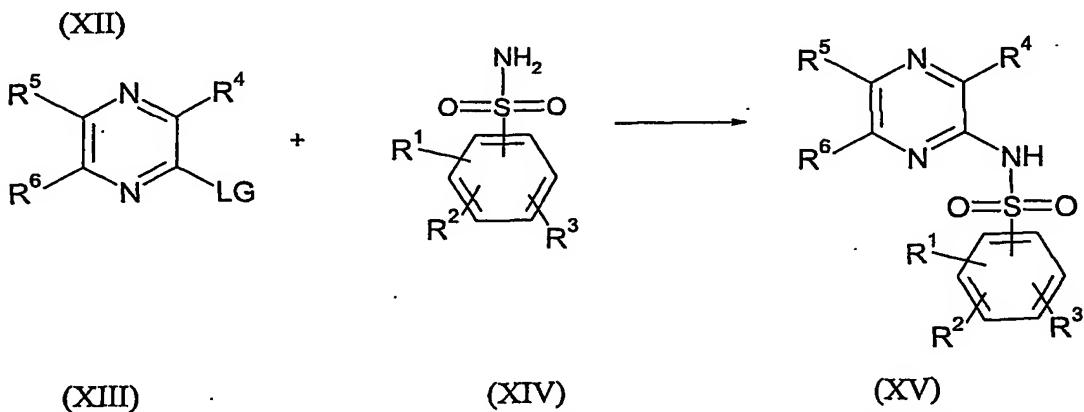
5 formula (I) where R⁵ or R⁶ is CH₂OH by oxidation using a suitable oxidising agent such as manganese dioxide or pyridinium chlorochromate (PCC) in a suitable solvent such as tetrahydrofuran or dichloromethane at a temperature of 0-50°C.

Compounds of formula (I) where R⁵ or R⁶ is CH(OH)R¹¹ or CH(OH)(C1-5)alkyl can be

10 prepared from compounds of formula (I) where R⁵ or R⁶ is CHO by reaction with a compound of formula (XII) where M is a metal such as magnesium or lithium in a suitable solvent such as tetrahydrofuran or diethyl ether at a temperature of 0-10°C

C₁₋₅ alkylM or R¹¹M

15



A compound of formula (XV) can be made by reacting a compound of formula (XIII),

20 where R⁴ is preferably chloro, bromo or alkoxy and LG is a suitable leaving group such as chloro or bromo, with a compound of formula (XIV) using a suitable base such as potassium carbonate or caesium carbonate in a suitable solvent such as N,N-dimethylformamide at a temperature of 40-90°C

Intermediate compounds of formula (II) and (III) can be prepared using standard chemistry 25 or are available commercially.

It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl or amino groups in the starting reagents or intermediate compound may need to be protected by protecting groups. Thus, 30 the preparation of the compound of formula (I) may involve, at an appropriate stage, the

removal of one or more protecting groups. The protection and deprotection of functional groups is fully described in 'Protective Groups in Organic Chemistry', edited by J. W. F. McOmie, Plenum Press (1973), and 'Protective Groups in Organic Synthesis', 2nd edition, T. W. Greene & P. G. M. Wuts, Wiley-Interscience (1991).

5 The compounds of formula (I) above may be converted to a pharmaceutically acceptable salt or solvate thereof, preferably a basic addition salt such as sodium, potassium, calcium, aluminium, lithium, magnesium, zinc, benzathine, chloroprocaine, choline, diethanolamine, ethanolamine, ethyldiamine, meglumine, tromethamine or procaine, or an 10 acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate.

Certain compounds of formula (II) and (III) are believed to be novel and form a further aspect of the invention.

15 The compounds of formula (I) above may be converted to a pharmaceutically acceptable salt or solvate thereof, preferably a basic addition salt such as sodium, potassium, calcium, aluminium, lithium, magnesium, zinc, benzathine, chloroprocaine, choline, diethanolamine, ethanolamine, ethyldiamine, meglumine, tromethamine or procaine, or an 20 acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate.

The compounds of formula (I) has activity as pharmaceuticals, in particular as modulators 25 of chemokine receptor (especially CCR4) activity, and may be used in the treatment (therapeutic or prophylactic) of conditions/diseases in human and non-human animals which are exacerbated or caused by excessive or unregulated production of chemokines. Examples of such conditions/diseases include:

(1) (the respiratory tract) obstructive airways diseases including chronic 30 obstructive pulmonary disease (COPD); asthma, such as bronchial, allergic, intrinsic, extrinsic and dust asthma, particularly chronic or inveterate asthma (e.g. late asthma and airways hyper-responsiveness); bronchitis; acute, allergic, atrophic rhinitis and chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca and rhinitis medicamentosa; 35 membranous rhinitis including croupous, fibrinous and pseudomembranous rhinitis and scrofulous rhinitis; seasonal rhinitis including rhinitis nervosa

(hay fever) and vasomotor rhinitis; sarcoidosis, farmer's lung and related diseases, fibroid lung and idiopathic interstitial pneumonia;

5 (2) (bone and joints) gout, rheumatoid arthritis, seronegative spondyloarthropathies (including ankylosing spondylitis, psoriatic arthritis and Reiter's disease), Behcet's disease, Sjogren's syndrome and systemic sclerosis;

10 (3) (skin) pruritis, scleroderma, otitus, psoriasis, atopical dermatitis, contact dermatitis and other eczematous dermatides, seborrhoetic dermatitis, Lichen planus, Pemphigus, bullous Pemphigus, Epidermolysis bullosa, urticaria, angiodermas, vasculitides, erythemas, cutaneous eosinophilias, uveitis, Alopecia areata and vernal conjunctivitis, lupus;

15 (4) (gastrointestinal tract) Coeliac disease, proctitis, eosinopilic gastro-enteritis, mastocytosis, inflammatory bowel diseases such as Crohn's disease, ulcerative colitis, ileitis and enteritis, food-related allergies which have effects remote from the gut, e.g., migraine, rhinitis and eczema;

20 (5) (central and peripheral nervous system) Neurodegenerative diseases and dementia disorders, e.g. Alzheimer's disease, amyotrophic lateral sclerosis and other motor neuron diseases, Creutzfeldt-Jacob's disease and other prion diseases, HIV encephalopathy (AIDS dementia complex), Huntington's disease, frontotemporal dementia, Lewy body dementia and vascular dementia; polyneuropathies, e.g. Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy, multifocal motor neuropathy, plexopathies; CNS demyelination, e.g. multiple sclerosis, acute disseminated/haemorrhagic encephalomyelitis, and subacute sclerosing panencephalitis; neuromuscular disorders, e.g. myasthenia gravis and Lambert-Eaton syndrome; spinal disorders, e.g. tropical spastic paraparesis, and stiff-man syndrome; paraneoplastic syndromes, e.g. cerebellar degeneration and encephalomyelitis; CNS trauma; migraine; stroke and correctum diseases such as meningitis

25 (6) (other tissues and systemic disease) hepatitis, vasculitis, spondyloarthropathies, vaginitis, glomerulonephritis, myositis, atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), lupus erythematosus,

systemic lupus, erythematosus, Hashimoto's thyroiditis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, lepromatous leprosy, and idiopathic thrombocytopenia pupura; post-operative adhesions, and sepsis.

5

- (7) (allograft and xenograft rejection) acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin and cornea; and chronic graft versus host disease;
- 10 (8) Cancer, carcinoma & tumour metastasis, including that of the bladder, breast, colon, kidney, liver, lung, ovary, pancreas, stomach, cervix, thyroid and skin, especially non-small cell lung cancer (NSCLC), malignant melanoma, prostate cancer and squamous sarcoma. Hematopoietic tumors of lymphoid lineage, including acute lymphocytic leukemia, B cell lymphoma and Burkitts lymphoma, Hodgkins Lymphoma, Acute Lymphoblastic Leukemia. Hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias and promyelocytic leukemia. Tumors of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma, and other tumors, including melanoma, seminoma, tetratocarcinoma, neuroblastoma and glioma.
- 15 (9) All diseases that result from a general imbalance of the immune system and resulting in increased atopic inflammatory reactions.
- 20 (10) Cystic fibrosis, re-perfusion injury in the heart, brain, peripheral limbs and other organs.
- 25 (11) Burn wounds & chronic skin ulcers
- 30 (12) Reproductive Diseases (e.g. Disorders of ovulation, menstruation and implantation, Pre-term labour, Endometriosis)
- 35 (13) thrombosis
- (14) infectious diseases such as HIV infection and other viral infections, bacterial infections.

Thus, the present invention provides a compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

5 Preferably the compound of the invention are used to treat diseases in which the chemokine receptor belongs to the CC chemokine receptor subfamily, more preferably the target chemokine receptor is the CCR4 receptor.

10 Particular conditions which can be treated with the compound of the invention are asthma, rhinitis and inflammatory skin disorders, diseases in which there are raised TARC, MDC or CCR4 levels. It is preferred that the compound of the invention is used to treat asthma and rhinitis, especially asthma.

15 In a further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

20 In a still further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for the treatment of human diseases or conditions in which modulation of chemokine receptor activity, particularly CCR4 activity, is beneficial.

25 In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

30 The invention still further provides a method of treating a chemokine mediated disease wherein the chemokine binds to a chemokine (especially CCR4) receptor, which comprises administering to a patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined.

35 The invention also provides a method of treating a respiratory disease, such as asthma and rhinitis, especially asthma, in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated.

5 The compound of formula (I) and pharmaceutically acceptable salts and solvates thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt/solvate (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably 10 comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

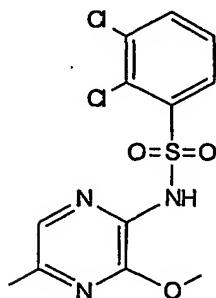
15 The present invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

20 The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined, with a pharmaceutically acceptable adjuvant, diluent or carrier.

25 The pharmaceutical compositions may be administered topically (e.g. to the lung and/or airways or to the skin) in the form of solutions, suspensions, heptafluoroalkane aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules, or by parenteral administration in the form of solutions or suspensions, or by subcutaneous administration or by rectal administration in the form of suppositories or transdermally. Preferably the compound of the invention is administered orally.

30 In a further aspect, the present invention provides the use of a compound or formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy in combination with drugs used to treat asthma and rhinitis (such as inhaled and oral steroids, inhaled β 2-receptor agonists and 35 oral leukotriene receptor antagonists).

The following examples illustrate the invention.

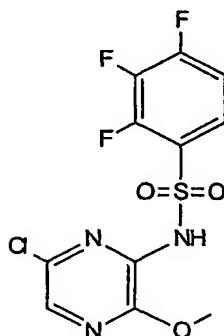
Example 1**2,3-Dichloro-N-(3-methoxy-5-methyl-2-pyrazinyl)-benzenesulphonamide**

5 Sodium hydride (0.1g of 60%) was added to 3-methoxy-5-methyl-2-pyrazinamine (0.07g) in 1,2-dimethoxyethane (3mL) under nitrogen at room temperature. After 1 hour at 50°, 2,3-dichlorobenzenesulphonyl chloride (0.15g) was added. After stirring for 30 minutes, 5% aqueous citric acid was added and the product extracted with ethyl acetate (X3). The combined extracts were washed with saturated brine, dried (MgSO_4) and the solvent was 10 evaporated. Chromatography on silica eluting with dichloromethane/methanol mixtures gave the title compound as a white solid (0.08g).

m/e 346/8/350 ($\text{M}-1^+$, 100%)

^1H NMR ($\text{D}_6\text{-DMSO}$) δ 11.27 (1H, s), 8.06 (1H, d), 7.93 (1H, d), 7.60-7.55 (1H, br s), 7.58 (1H, t), 3.87 (3H, s), 2.28 (3H, s).

15

Example 2***N*-(6-Chloro-3-methoxy-2-pyrazinyl)-2,3,4-trifluorobenzenesulphonamide**

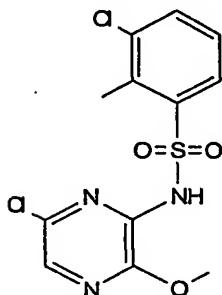
20 Prepared by the method of Example 1 (reaction performed at room temperature) using 6-chloro-3-methoxy-2-pyrazinamine (0.16g) and 2,3,4-trifluorobenzenesulphonyl chloride (0.25g). Yield 0.08g.

m/e 352/4 ($\text{M}-1^+$, 100%)

¹H NMR (D6-DMSO) δ 7.93-7.80 (1H, m), 7.89 (1H, s), 7.60-7.50 (1H, m), 3.91 (3H, s).

Example 3

3-Chloro-N-(6-chloro-3-methoxy-2-pyrazinyl)-2-methylbenzenesulphonamide



5 Prepared by the method of Example 1 (reaction performed at room temperature) using 6-chloro-3-methoxy-2-pyrazinamine (0.16g) and 3-chloro-2-methylbenzenesulphonyl chloride (0.23g). Yield 0.15g.
 m/e 346/8/50 (M-1⁺, 100%)

10 ¹H NMR (D6-DMSO) δ 8.05 (1H, d), 7.85 (1H, s), 7.75 (1H, d), 7.47 (1H, t), 3.92 (3H, s), 2.66 (3H, s).

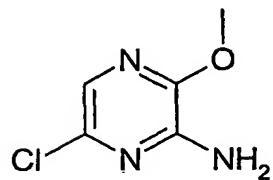
Example 4

2,3-Dichloro-N-(6-chloro-3-methoxy-2-pyrazinyl)benzenesulphonamide

15 a) 3-Bromo-6-chloro-2-pyrazinamine

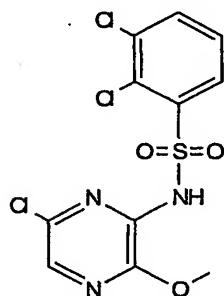
N-bromosuccinamide (6.9g) was added portionwise over 0.5h to a stirred solution of 6-chloro-2-pyrazinamine (5.0g) in chloroform (200mL) heated under reflux. After the addition was complete the reaction mixture was allowed to cool, washed with water and evaporated to give a 3:1 mixture of 5-bromo-6-chloro-2-pyrazinamine and the subtitle compound which were separated by silica gel chromatography eluting with dichloromethane. Yield 2.0g. Used directly.

25 b) 6-Chloro-3-methoxy-2-pyrazinamine and 3-bromo-6-methoxy-2-pyrazinamine



3-Bromo-6-chloro-2-pyrazinamine (1.0g), sodium methoxide (3mL of 25% solution in methanol) and methanol (10mL) were heated at reflux for 3 hours. The solvent was evaporated and the residue was dissolved in ethyl acetate and brine. The organic layer was separated dried (MgSO_4) and the solvent was evaporated to give a mixture of the sub-title compounds (ratio 10:1). Purification was by silica gel chromatography eluting with dichloromethane. Yield 0.5g. Used directly.

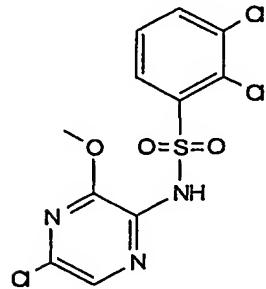
c) 2,3-Dichloro-*N*-(6-Chloro-3-methoxy-2-pyrazinyl)benzenesulphonamide



Prepared by the method of Example 1 (reaction performed at room temperature) using 6-chloro-3-methoxy-2-pyrazinamine (0.24g) and 2,3-dichlorobenzenesulphonyl chloride (0.32g). Yield 0.24g.
 m/e 366/8/370/2 ($\text{M}-1^+$, 100%)
¹H NMR (D6-DMSO) δ 8.14 (1H, d), 7.96 (1H, d), 7.89 (1H, s), 7.62 (1H, t), 3.91 (3H, s).

Example 5

2,3-Dichloro-*N*-(5-chloro-3-methoxy-2-pyrazinyl)benzenesulphonamide



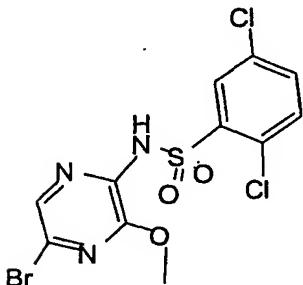
Prepared by the method of Example 1 (reaction performed at room temperature) using 5-chloro-3-methoxy-2-pyrazinamine (0.1g) and 2,3-dichlorobenzenesulphonyl chloride (0.15g). Yield 0.05g.

m/e 366/8/370/2 (M-1⁺, 100%)

5 ¹H NMR (D6-DMSO) δ 8.15 (1H, d), 7.93 (1H, d), 7.79 (1H, s), 7.58 (1H, t), 3.93 (3H, s).

Example 6

N-(5-Bromo-3-methoxy-2-pyrazinyl)-2,5-dichlorobenzenesulphonamide



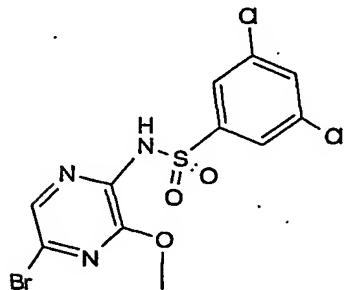
10 Prepared by the method of Example 1 (reaction performed at room temperature) using 5-bromo-3-methoxy-2-pyrazinamine (0.2g) and 2,5-dichlorobenzenesulphonyl chloride (0.24g). Yield 0.14g.

m/e 410/2/4/6 (M-1⁺, 100%)

15 ¹H NMR (D6-DMSO) δ 8.04 (1H, d), 7.86 (1H, s), 7.73 (1H, dd), 7.66 (1H, dd), 3.91 (3H, s).

Example 7

N-(5-Bromo-3-methoxy-2-pyrazinyl)-3,5-dichlorobenzenesulphonamide



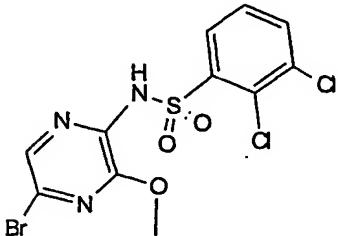
20 Prepared by the method of Example 1 (reaction performed at room temperature) using 5-bromo-3-methoxy-2-pyrazinamine (0.2g) and 3,5-dichlorobenzenesulphonyl chloride (0.24g). Yield 0.012g.

m/e 410/2/4/6 (M-1⁺, 100%)

¹H NMR (D6-DMSO) δ 7.96-7.91 (4H, m), 3.93 (3H, s).

Example 8

N-(5-Bromo-3-methoxy-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide



5

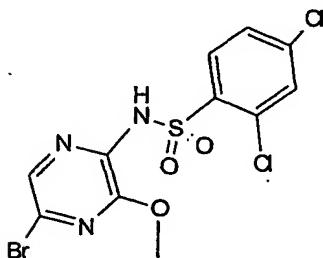
Prepared by the method of Example 1 (reaction performed at room temperature) using 5-bromo-3-methoxy-2-pyrazinamine (0.1g) and 2,3-dichlorobenzenesulphonyl chloride (0.2g). Yield 0.045g.

m/e 410/2/4/6 (M-1⁺, 100%)

10 ¹H NMR (D6-DMSO) δ 8.06 (1H, dd), 7.93 (1H, dd), 7.82 (1H, s), 7.57 (1H, t), 3.92 (3H, s).

Example 9

N-(5-Bromo-3-methoxy-2-pyrazinyl)-2,4-dichlorobenzenesulphonamide



15

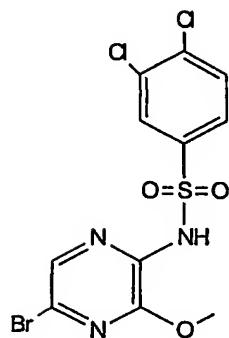
Prepared by the method of Example 1 (reaction performed at room temperature) using 5-bromo-3-methoxy-2-pyrazinamine (0.2g) and 2,4-dichlorobenzenesulphonyl chloride (0.24g). Yield 0.059g.

m/e 410/2/4/6 (M-1⁺, 100%)

20 ¹H NMR (D6-DMSO) δ 8.07 (1H, d), 7.85 (2H, d), 7.64 (1H, dd), 3.92 (3H, s).

Example 10

N-(5-Bromo-3-methoxy-2-pyrazinyl)-3,4-dichlorobenzenesulphonamide



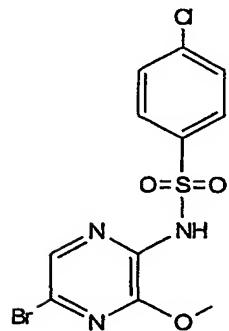
Prepared by the method of Example 1 (reaction performed at room temperature) using 5-bromo-3-methoxy-2-pyrazinamine (0.15g) and 3,4-dichlorobenzenesulphonyl chloride (0.15g). Yield 0.09g.

5 m/e 410/2/4/6 (M-1⁺, 100%)

¹H NMR (D6-DMSO) δ 8.14 (1H, s), 8.00-7.85 (3H, m), 3.94 (3H, s).

Example 11

N-(5-Bromo-3-methoxy-2-pyrazinyl)-4-chlorobenzenesulphonamide



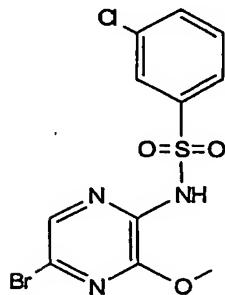
10

Prepared by the method of Example 1 (reaction performed at room temperature) using 5-bromo-3-methoxy-2-pyrazinamine (0.1g) and 4-chlorobenzenesulphonyl chloride (0.13g).

Yield 0.13g.

m/e 376/8/380 (M-1⁺, 100%)

15 ¹H NMR (D6-DMSO) δ 11.3 (1H, br s), 7.97 (2H, d), 7.91 (1H, s), 7.66 (2H, d), 3.93 (3H, s).

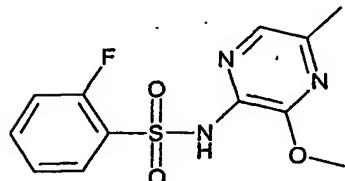
Example 12**N-(5-Bromo-3-methoxy-2-pyrazinyl)-3-chlorobenzenesulphonamide**

Prepared by the method of Example 1 (reaction performed at room temperature) using 5-bromo-3-methoxy-2-pyrazinamine (0.1g) and 3-chlorobenzenesulphonyl chloride (0.13g).

Yield 0.14g.

m/e 376/8/380 (M-1⁺, 100%)

¹H NMR (D6-DMSO) δ 8.00-7.90 (3H, m), 7.75 (1H, d), 7.64 (1H, t), 3.94 (3H, s).

Example 13**N-(3-Methoxy-5-methyl-2-pyrazinyl)-2-fluorobenzenesulphonamide**

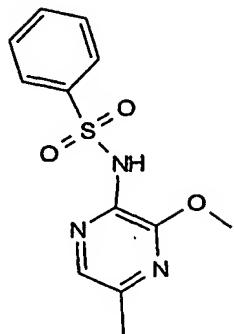
Prepared by the method of Example 1 using 3-methoxy-5-methyl-2-pyrazinamine and 2-fluorobenzenesulphonyl chloride.

m/e 298 (M+1⁺, 100%)

¹H NMR (D6-DMSO) δ 11.05 (1H, br s), 7.85-7.95 (1H, m), 7.65-7.75 (1H, m), 7.50-7.60 (1H, m), 7.35-7.45 (1H, m), 3.90 (3H, s), 2.30 (3H, s).

MP 150-152°C

Example 14**N-(3-Methoxy-5-methyl-2-pyrazinyl)benzenesulphonamide**



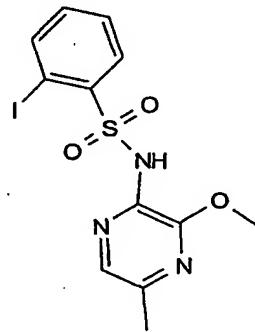
Prepared by the method of Example 1 using 3-methoxy-5-methyl-2-pyrazinamine and benzenesulphonyl chloride

MP 138-139°C

5

Example 15

N-(3-Methoxy-5-methyl-2-pyrazinyl)-2-iodobenzenesulphonamide



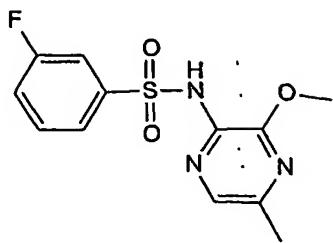
Prepared by the method of Example 1 using 3-methoxy-5-methyl-2-pyrazinamine and 2-iodobenzenesulphonyl chloride.

10 ^1H NMR (D6-DMSO) δ 10.75 (1H, br s), 8.05-8.15 (2H, m), 7.65-7.75 (2H, m), 7.30 (1H, dt), 3.90 (3H, s), 2.30 (3H, s).

MP 140-141°C

15 **Example 16**

N-(3-Methoxy-5-methyl-2-pyrazinyl)-3-fluorobenzenesulphonamide



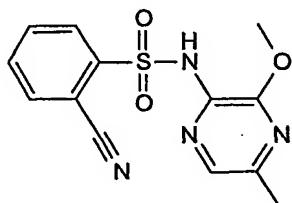
Prepared by the method of Example 1 using 3-methoxy-5-methyl-2-pyrazinamine and 3-fluorobenzenesulphonyl chloride.

MP 95-97°C

5

Example 17

2-[(3-Methoxy-5-methyl-2-pyrazinyl)amino]sulphonylbenzonitrile



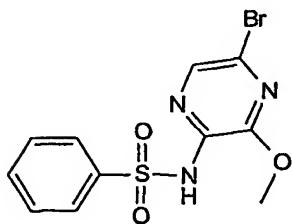
Prepared by the method of Example 1 using 3-methoxy-5-methyl-2-pyrazinamine and 2-cyanobenzenesulphonyl chloride.

10 m/e 305 (M+1⁺, 100%)

¹H NMR (D6-DMSO) δ 8.15 (1H, dd), 8.05 (1H, dd), 7.85 (1H, dt), 7.80 (1H, dt), 7.60 (1H, s), 3.85 (3H, s), 2.30 (3H, s).

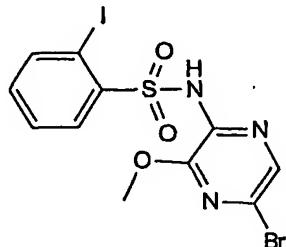
15 **Example 18**

N-(5-Bromo-3-methoxy-2-pyrazinyl)benzenesulphonamide



Prepared by the method of Example 1 (reaction performed at room temperature) using 5-bromo-3-methoxy-2-pyrazinamine and benzenesulphonyl chloride

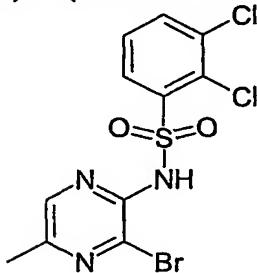
20 m/e 344 (M+1⁺, 100%)

Example 19***N*-(5-Bromo-3-methoxy-2-pyrazinyl)2-iodobenzenesulphonamide**

Prepared by the method of Example 1 (reaction performed at room temperature) using 5-bromo-3-methoxy-2-pyrazinamine and 2-iodobenzenesulphonyl chloride.

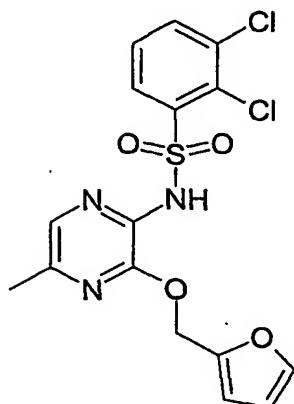
m/e 470 (M+1⁺, 100%)

¹H NMR (D6-DMSO) δ 11.30 (1H, br s), 8.0-8.1 (2H, m), 7.80 (1H, s), 7.60 (1H, dt), 7.30 (1H, dt), 3.95 (3H, s).

Example 20**2,3-Dichloro-*N*-[3-(2-furanylmethoxy)-5-methyl-2-pyrazinyl]benzenesulphonamide****a) *N*-(3-Bromo-5-methyl-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide**

Prepared by the method of Example 1 using 3-bromo-5-methyl-2-pyrazinamine (0.84g) and 2,3-dichlorobenzenesulphonyl chloride (1.1g). Yield 0.92g.

b) 2,3-Dichloro-*N*-[3-(2-furanylmethoxy)-5-methyl-2-pyrazinyl]benzenesulphonamide

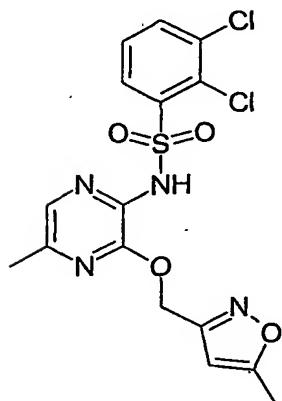


Sodium hydride (0.04g of a 60% dispersion in oil) was added to furfurylalcohol (0.034g) in 1,2-dimethoxyethane (1mL). After 5 minutes *N*-(3-Bromo-5-methyl-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide (Example 20 part a) (0.1g) was added and the mixture heated at 40 °C. After 16h, 5% aqueous citric acid (10mL) was added and the mixture extracted with ethyl acetate (2x50mL). The combined extracts were washed with brine, dried (MgSO_4) and the solvent evaporated. Chromatography on silica gel eluting with dichloromethane gave the title compound as a white solid (0.02g)
 m/e 412 ($\text{M}-1^+$, 100%)

10 ^1H NMR (D6-DMSO) δ 11.33 (1H, br s), 8.01 (1H, d), 7.90 (1H, d), 7.70 (1H, s), 7.62 (1H, br s), 7.54 (1H, t), 6.61-6.58 (1H, m), 6.50-6.45 (1H, m), 5.33 (2H, s), 2.32 (3H, s)
 MP 127-129°C

Example 21

15 2,3-Dichloro-*N*-[5-methyl-3-(5-methyl-3-isoxazolylmethoxy)-2-pyrazinyl]benzenesulphonamide



Prepared by the method of Example 20 using (5-methyl-3-isoxazolyl)methanol (0.05g) and 20 *N*-(3-bromo-5-methyl-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide (0.1g). Yield 0.05g.

m/e 429 ($M+1^+$, 100%)

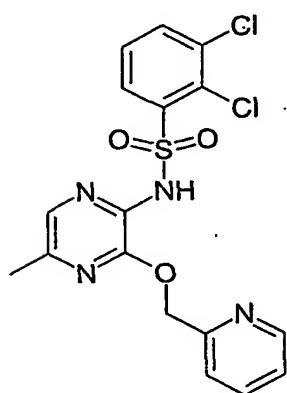
^1H NMR (D6-DMSO) δ 11.39 (1H, br s), 8.03 (1H, d), 7.91 (1H, d), 7.64 (1H, br s), 7.47 (1H, t), 6.33 (1H, s), 5.37 (2H, s), 2.41 (3H, s), 2.29 (3H, s)

MP 155-156°C

5

Example 22

2,3-Dichloro-N-[5-methyl-3-(2-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide



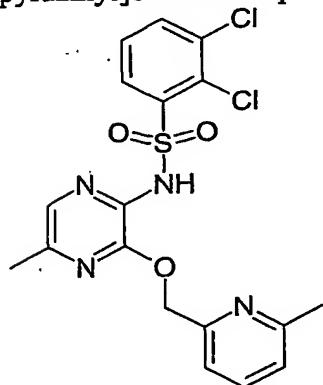
10 Prepared by the method of Example 20 using pyridine-2-methanol (0.05g) and *N*-(3-bromo-5-methyl-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide (0.1g). Yield 0.07g.
m/e 425 ($M+1^+$, 100%)

^1H NMR (D6-DMSO) δ 8.57-8.54 (1H, m), 8.05 (1H, d), 7.89 (1H, d), 7.83 (1H, dt), 7.65-7.50 (2H, m), 7.56 (1H, t), 7.35-7.30 (1H, m), 5.44 (2H, s), 2.26 (3H, s)

15

Example 23

2,3-Dichloro-N-[5-methyl-3-(6-methyl-2-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide



20 Prepared by the method of Example 20 using 6-methylpyridine-2-methanol (0.05g) and *N*-(3-bromo-5-methyl-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide (0.1g). Yield 0.023g.

m/e 439 ($M+1^+$, 100%)

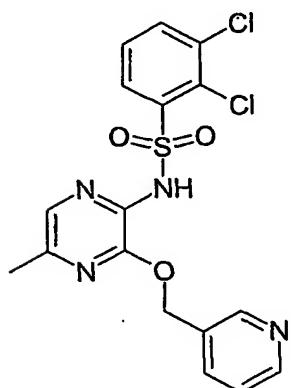
^1H NMR (D6-DMSO) δ 8.05 (1H, dd), 7.89 (1H, dd), 7.70 (1H, t), 7.59 (1H, br s), 7.54 (1H, t), 7.34 (1H, d), 7.19 (1H, d), 5.39 (2H, s), 2.47 (3H, s), 2.26 (3H, s)

MP 164-165°C

5

Example 24

2,3-Dichloro-N-[5-methyl-3-(3-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide



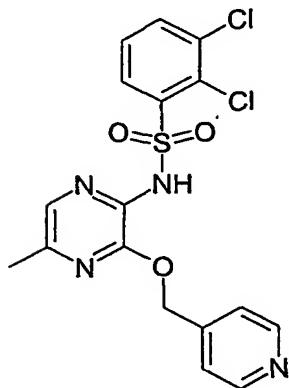
10 Prepared by the method of Example 20 using pyridine-3-methanol (0.05g) and *N*-(3-bromo-5-methyl-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide (0.1g). Yield 0.023g.
m/e 425 ($M+1^+$, 100%)

^1H NMR (D6-DMSO) δ 8.74 (1H, d), 8.55 (1H, dd), 8.03 (1H, dd), 7.95-7.85 (2H, m), 7.59 (1H, br s), 7.54 (1H, t), 7.42 (1H, dd), 5.41 (2H, s), 2.29 (3H, s)

15 MP 160-161°C

Example 25

2,3-Dichloro-N-[5-methyl-3-(4-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide



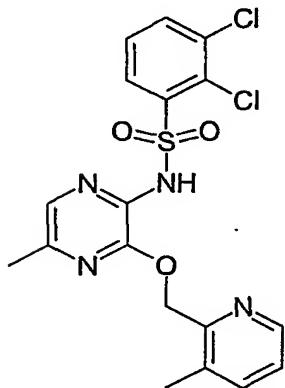
20

Prepared by the method of Example 20 using pyridine-4-methanol (0.05g) and *N*-(3-bromo-5-methyl-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide (0.1g). Yield 0.009g. m/e 425 (M+1⁺, 100%)

¹H NMR (D6-DMSO) δ 8.57 (2H, d), 8.05 (1H, dd), 7.89 (1H, dd), 7.60 (1H, s), 7.55 (1H, t), 7.50 (2H, d), 5.43 (2H, s), 2.26 (3H, s)
5 MP 183-184°C

Example 26

10 2,3-Dichloro-*N*-[5-methyl-3-(3-methyl-2-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide



Prepared by the method of Example 20 using 3-methylpyridine-2-methanol (0.05g) and *N*-(3-bromo-5-methyl-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide (0.1g). Yield 0.021g.

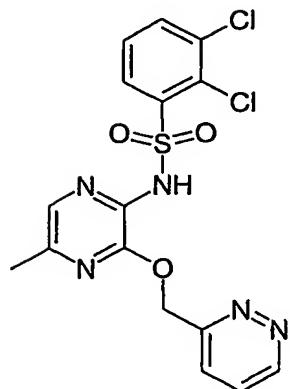
15 m/e 439 (M+1⁺, 100%)

¹H NMR (D6-DMSO) δ 8.36 (1H, d), 8.05 (1H, dd), 7.83 (1H, dd), 7.64 (1H, d), 7.60 (1H, br s), 7.49 (1H, t), 7.31 (1H, dd), 5.40 (2H, s), 2.33 (3H, s), 2.29 (3H, s)

MP 137-138°C

20 **Example 27**

2,3-Dichloro-*N*-[5-methyl-3-(3-pyridazinylmethoxy)-2-pyrazinyl]benzenesulphonamide



Prepared by the method of Example 20 using pyridazine-3-methanol (0.1g) and *N*-(3-bromo-5-methyl-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide (0.15g). Yield 0.038g. m/e 424 (M-1⁺, 100%)

5 ¹H NMR (D6-DMSO) δ 11.47 (1H, br s), 9.21 (1H, dd), 8.05 (1H, dd), 8.00-7.95 (1H, m), 7.88 (1H, d), 7.80-7.75 (1H, m), 7.62 (1H, br s), 7.54 (1H, t), 5.65 (2H, s), 2.27 (3H, s)
MP 119-124°C

Example 28

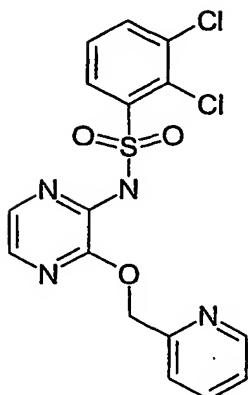
10 2,3-Dichloro-*N*-[3-(2-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide

a) 2,3-Dichloro-*N*-(3-chloro-2-pyrazinyl)benzenesulphonamide



15 2,3-Dichloropyrazine (2.6g), 2,3-dichlorobenzenesulphonamide (4.0g) and potassium carbonate (10.0g) in *N,N*-dimethylformamide (50mL) was heated at 75°C. After 16h, 5% aqueous citric acid (30mL) was added and the mixture extracted with ethyl acetate (2x100mL). The combined extracts were washed with brine, dried (MgSO₄) and the solvent evaporated. Chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound (1.5g).

20 b) 2,3-Dichloro-*N*-[3-(2-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide



Sodium hydride (0.05g of a 60% dispersion in oil) was added to pyridine-2-methanol (0.088g) in 1,2-dimethoxyethane (3.0mL). After 5 minutes, 2,3-dichloro-N-(3-chloro-2-pyrazinyl)benzenesulphonamide (0.1g) was added and the mixture heated at 70°C. After 5 4h, 5% aqueous citric acid (10mL) was added and the mixture extracted with ethyl acetate (2x50mL). The combined extracts were washed with brine, dried (MgSO_4) and the solvent evaporated. Chromatography on silica gel eluting with ethyl acetate/iso hexane mixtures gave the title compound as a white solid (0.06g).

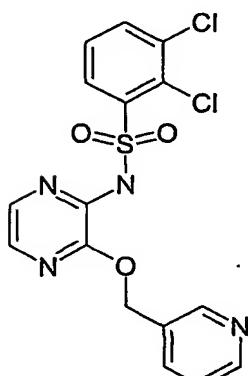
m/e 411 ($\text{M}+1^+$, 100%)

10 ^1H NMR (D6-DMSO) δ 8.57 (1H, d), 8.13 (1H, d), 7.93 (1H, d), 7.90-7.75 (2H, m), 7.75-7.65 (1H, m), 7.65-7.55 (2H, m), 7.40-7.30 (1H, m), 5.49 (2H, s)

MP 167-168°C

Example 29

15 2,3-Dichloro-N-[3-(3-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide



Prepared by the method of Example 28 using pyridine-3-methanol (0.09g) and 2,3-dichloro-N-(3-chloro-2-pyrazinyl)benzenesulphonamide (0.1g). Yield 0.042g.

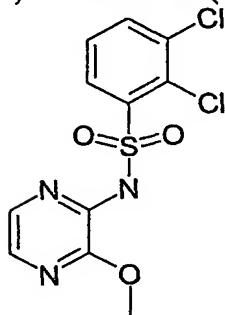
20 m/e 409 ($\text{M}-1^+$, 100%)

¹H NMR (CDCl₃) δ 8.70 (1H, s), 8.65 (1H, d), 8.28 (1H, dd), 7.79 (1H, d), 7.70-7.67 (2H, m), 7.61 (1H, d), 7.40-7.35 (2H, m), 5.45 (2H, s)

MP 138-139°C

5 **Example 30**

2,3-Dichloro-N-(3-methoxy-2-pyrazinyl)benzenesulphonamide



2,3-Dichloro-N-(3-chloro-2-pyrazinyl)benzenesulphonamide (Example 28 part a) (0.2g) in 10% sodium methoxide in methanol (10mL) was heated at 85°C. After 4h, 5% aqueous citric acid (50mL) was added and the mixture extracted with ethyl acetate (2x150mL). The combined extracts were washed with brine, dried (MgSO₄) and the solvent evaporated. Chromatography on silica gel eluting with ethyl acetate/iso hexane mixtures gave the title compound as a white solid (0.12g)

m/e 334 (M+1⁺, 100%)

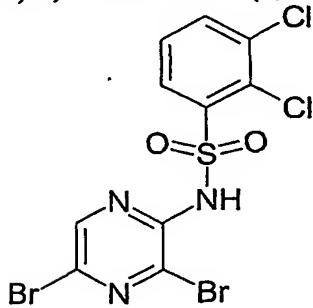
15 ¹H NMR (D6-DMSO) δ 11.54 (1H, br s), 8.10 (1H, d), 7.94 (1H, d), 7.85-7.75 (1H, m), 7.70-7.55 (1H, m), 7.59 (1H, t), 3.90 (3H, s)

MP 183-184°C

Example 31

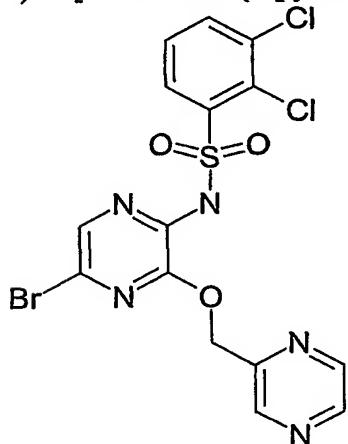
20 N-[5-Bromo-3-(2-pyrazinylmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide

a) 2,3-Dichloro-N-(3,5-dibromo-2-pyrazinyl)benzenesulphonamide



Prepared by the method of Example 1 (reaction performed at room temperature) using 3,5-dibromo-2-pyrazinamine (2.9g) and 2,3-dichloro benzenesulphonyl chloride (2.8g). Yield 4.4g.

b) *N*-(5-Bromo-3-(2-pyrazinylmethoxy)-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide



5 Sodium hydride (0.05g of a 60% dispersion in oil) was added to pyrazine-2-methanol (0.04g) in 1,2-dimethoxyethane (3ml). After 5 minutes, 2,3-Dichloro-*N*-(3,5-dibromo-2-pyrazinyl)benzenesulphonamide

10 (0.12g) was added. After 0.5h, 5% aqueous citric acid (10mL) was added and the mixture extracted with ethyl acetate (2x30mL). The combined extracts were washed with brine, dried ($MgSO_4$) and the solvent evaporated. Chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound as a white solid (0.06g).

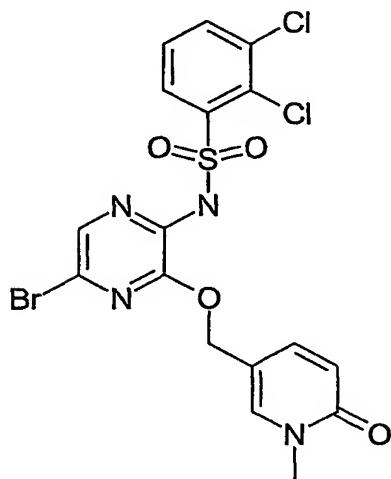
m/e 489 ($M-1^+$, 100%)

15 1H NMR (D6-DMSO) δ 9.00 (1H, s), 8.66 (2H, s), 8.08 (1H, dd), 7.92 (1H, dd), 7.91 (1H, s), 7.56 (1H, t), 5.53 (2H, s)

MP 207-209°C

Example 32

20 *N*-(5-Bromo-3-(1-methyl-6-oxo-1,6-dihydro-3-pyridinylmethoxy)-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide



Prepared by the method of Example 31 using 5-hydroxymethyl-1-methyl-1H-pyridin-2-one (0.1g) and 2,3-dichloro-N-(3,5-dibromo-2-pyrazinyl)benzenesulphonamide (0.16g). Yield 0.035g.

m/e 521 (M+1⁺, 100%)

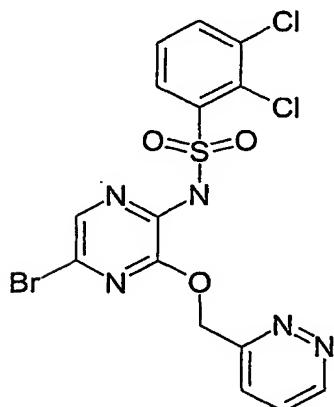
¹H NMR (D6-DMSO) δ 8.04 (1H, dd), 7.91 (1H, dd), 7.90-7.87 (2H, m), 7.60-7.50 (2H, m), 6.42 (1H, d), 5.10 (2H, s), 3.41 (3H, s)

MP 169-170°C

10

Example 33

N-[5-Bromo-3-(3-pyridazinylmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide



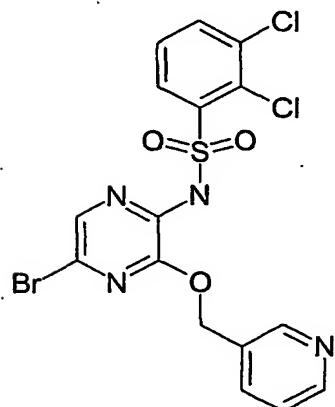
15 Prepared by the method of Example 31 using pyridazine-3-methanol (0.07g) and 2,3-dichloro-N-(3,5-dibromo-2-pyrazinyl)benzenesulphonamide (0.15g). Yield 0.06g.
m/e 489 (M-1⁺, 100%)

¹H NMR (D6-DMSO) δ 9.23 (1H, d), 8.08 (1H, dd), 7.99 (1H, dd), 7.92 (1H, dd), 7.91 (1H, s), 7.80 (1H, dd), 7.56 (1H, t), 5.67 (2H, s)

MP 115-120°C

5 **Example 34**

N-[5-Bromo-3-(3-pyridinylmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide

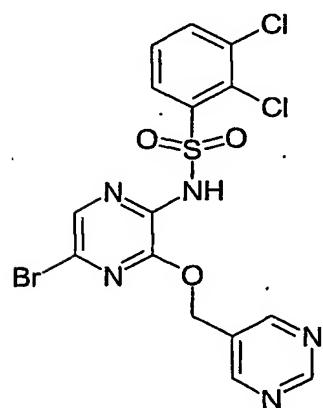


Prepared by the method of Example 31 using pyridine-3-methanol (0.44g) and 2,3-dichloro-*N*-(3,5-dibromo-2-pyrazinyl)benzenesulphonamide (1.0g). Yield 0.6g.
 10 m/e 491 (M+1⁺, 100%)
¹H NMR (D6-DMSO) δ 8.78 (1H, d), 8.58 (1H, dd), 8.06 (1H, d), 7.99 (1H, dt), 7.91 (1H, d), 7.88 (1H, s), 7.55 (1H, t), 7.55-7.50 (1H, m), 5.44 (2H, s)
 MP 204-206°C

15

Example 35

N-[5-Bromo-3-(5-pyrimidinylmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide



Prepared by the method of Example 31 using pyrimidine-5-methanol (0.035g) and 2,3-dichloro-*N*-(3,5-dibromo-2-pyrazinyl)benzenesulphonamide (0.16g). Yield 0.028g.

m/e 490 (M-1⁺, 100%)

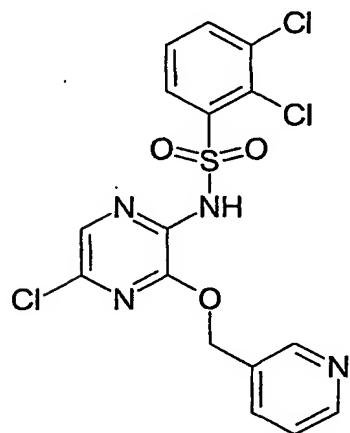
¹H NMR (D6-DMSO) δ 9.21 (1H, s), 9.02 (2H, s), 8.07 (1H, dd), 7.92 (1H, dd), 7.91 (1H, s), 7.56 (1H, t), 5.45 (2H, s)

MP 208-209°C

Example 36

N-[5-Chloro-3-(3-pyridinylmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide

10



Prepared by the method of Example 31 using pyridine-3-methanol (0.13g) and 2,3-dichloro-*N*-(3,5-dichloro-2-pyrazinyl)benzenesulphonamide (Example 74) (0.3g). Yield 0.19g.

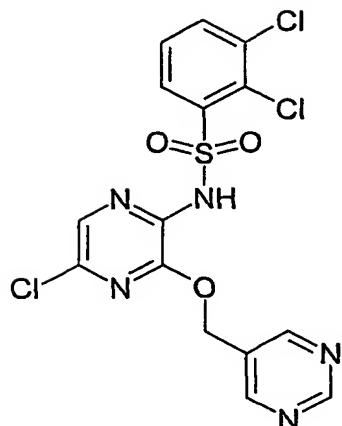
15 m/e 447 (M+1⁺, 100%)

¹H NMR (D6-DMSO) δ 8.78 (1H, s), 8.59 (1H, dd), 8.06 (1H, dd), 7.96 (1H, dt), 7.91 (1H, dd), 7.83 (1H, s), 7.55 (1H, t), 7.47 (1H, dd), 5.44 (2H, s)

MP 200-204°C

20 **Example 37**

N-[5-Chloro-3-(5-pyrimidinylmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide



Prepared by the method of Example 31 using pyrimidine-5-methanol (0.035g) and 2,3-dichloro-*N*-(3,5-dichloro-2-pyrazinyl)benzenesulphonamide (Example 74) (0.07g). Yield 0.015g.

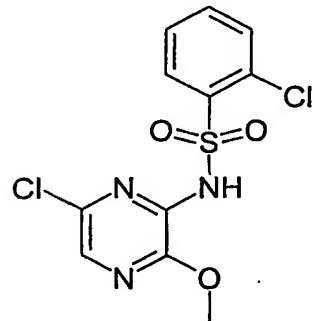
5 m/e 448 ($M+1^+$, 100%)

^1H NMR (D6-DMSO) δ 9.21 (1H, s), 9.02 (2H, s), 8.08 (1H, dd), 7.92 (1H, dd), 7.86 (1H, s), 7.56 (1H, t), 5.46 (2H, s)

MP 205-206°C

10 **Example 38**

2-Chloro-*N*-(6-chloro-3-methoxy-2-pyrazinyl)benzenesulphonamide



Prepared by the method of Example 1 (reaction performed at room temperature) using 6-chloro-3-methoxy-2-pyrazinamine (0.1g) and 2-chlorobenzenesulphonyl chloride (0.13g).

15 Yield 0.11g.

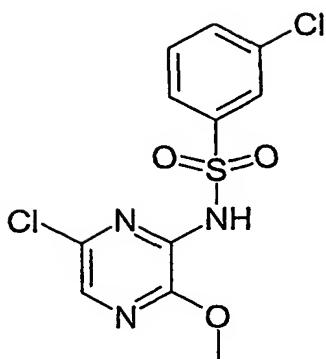
m/e 332 ($M-1^+$, 100%)

^1H NMR (D6-DMSO) δ 8.15 (1H, d), 7.86 (1H, s), 7.70-7.50 (3H, m), 3.91 (3H, s)

MP 172-173°C

20 **Example 39**

3-Chloro-*N*-(6-chloro-3-methoxy-2-pyrazinyl)benzenesulphonamide



Prepared by the method of Example 1 (reaction performed at room temperature) using 6-chloro-3-methoxy-2-pyrazinamine (0.1g) and 3-chlorobenzenesulphonyl chloride (0.13g).

5 Yield 0.14g.

m/e 332 (M-1⁺, 100%)

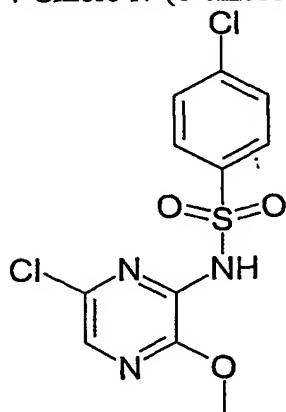
¹H NMR (D6-DMSO) δ 8.05 (1H, d), 7.93 (1H, dd), 7.90 (1H, s), 7.76 (1H, dd), 7.65 (1H, t) 3.92 (3H, s)

MP 126-127°C

10

Example 40

4-Chloro-N-(6-chloro-3-methoxy-2-pyrazinyl)benezenesulphonamide



Prepared by the method of Example 1 (reaction performed at room temperature) using 6-chloro-3-methoxy-2-pyrazinamine (0.1g) and 4-chlorobenzenesulphonyl chloride (0.13g).

15 Yield 0.13g.

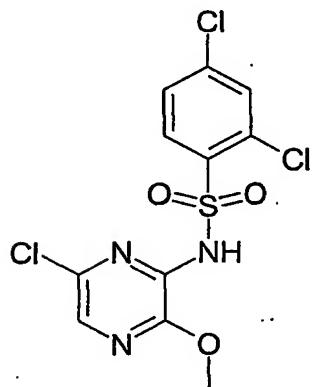
m/e 332 (M-1⁺, 100%)

¹H NMR (D6-DMSO) δ 7.99 (2H, dt), 7.89 (1H, s), 7.70 (2H, dt), 3.92 (3H, s)

MP 174-175°C

20

Example 41

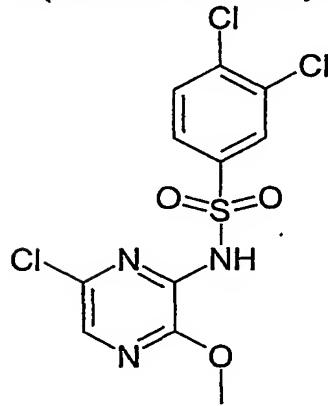
N-(6-Chloro-3-methoxy-2-pyrazinyl)-2,4-dichlorobenezenesulphonamide

Prepared by the method of Example 1 (reaction performed at room temperature) using 6-chloro-3-methoxy-2-pyrazinamine (0.05g) and 2,4-dichlorobenezenesulphonyl chloride (0.1g). Yield 0.07g.

m/e 368 (M-1⁺, 100%)

¹H NMR (D6-DMSO) δ 8.13 (1H, d), 7.86 (1H, s), 7.85 (1H, d), 7.70 (1H, dd), 3.91 (3H, s)

MP 189-190°C

Example 42*N*-(6-Chloro-3-methoxy-2-pyrazinyl)-3,4-dichlorobenezenesulphonamide

Prepared by the method of Example 1 (reaction performed at room temperature) using 6-chloro-3-methoxy-2-pyrazinamine (0.05g) and 3,4-dichlorobenezenesulphonyl chloride (0.09g). Yield 0.08g.

m/e 368 (M-1⁺, 100%)

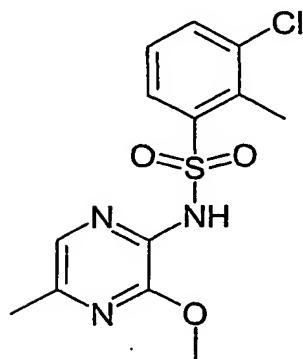
¹H NMR (D6-DMSO) δ 8.21 (1H, s), 7.93-7.90 (3H, m), 3.92 (3H, s)

MP 176-177°C

Example 43

3-Chloro-N-(3-methoxy-5-methyl-2-pyrazinyl)-2-methylbenzenesulphonamide

5



Prepared by the method of Example 1 using 3-methoxy-5-methyl-2-pyrazinamine (0.1g) and 3-chloro-2-methylbenzenesulphonyl chloride (0.19g). Yield 0.08g.

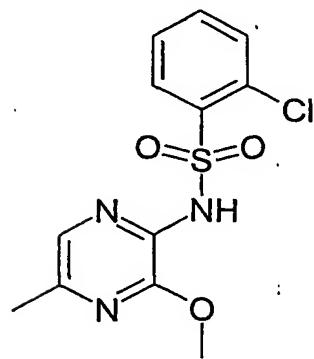
m/e 328 (M+1⁺, 100%)

10 ¹H NMR (D6-DMSO) δ 11.09 (1H, br s), 7.95 (1H, d), 7.72 (1H, d), 7.54 (1H, br s), 7.41 (1H, t), 3.88 (3H, s), 2.64 (3H, s), 2.27 (3H, s)

MP 133-135°C

Example 44

15 2-Chloro-N-(3-methoxy-5-methyl-2-pyrazinyl)benzenesulphonamide



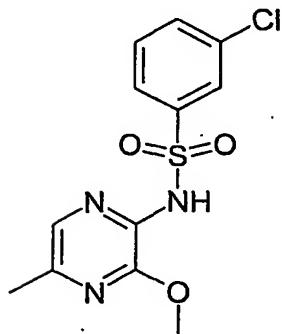
Prepared by the method of Example 1 using 3-methoxy-5-methyl-2-pyrazinamine (0.1g) and 2-chlorobenzenesulphonyl chloride (0.15g). Yield 0.06g.

m/e 314 (M+1⁺, 100%)

¹H NMR (D6-DMSO) δ 11.07 (1H, br s), 8.06 (1H, d), 7.69-7.46 (4H, m), 3.90 (3H, s), 2.24 (3H, s)

Example 45

5 3-Chloro-N-(3-methoxy-5-methyl-2-pyrazinyl)benezenesulphonamide



Prepared by the method of Example 1 using 3-methoxy-5-methyl-2-pyrazinamine (0.1g) and 3-chlorobenzenesulphonyl chloride (0.18g). Yield 0.042g.

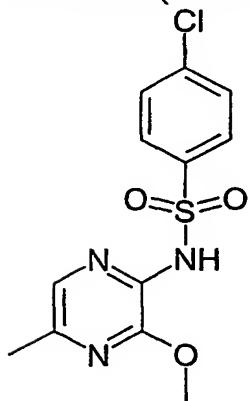
10 m/e 314 (M+1⁺, 100%)

¹H NMR (D6-DMSO) δ 10.89 (1H, br s), 7.97 (1H, d), 7.92 (1H, d), 7.73 (1H, d), 7.65-7.58 (2H, m), 3.90 (3H, s), 2.29 (3H, s)

MP 123-125°C

15 **Example 46**

4-Chloro-N-(3-methoxy-5-methyl-2-pyrazinyl)benezenesulphonamide



Prepared by the method of Example 1 using 3-methoxy-5-methyl-2-pyrazinamine (0.1g) and 4-chlorobenzenesulphonyl chloride (0.18g). Yield 0.06g.

20 m/e 314 (M+1⁺, 100%)

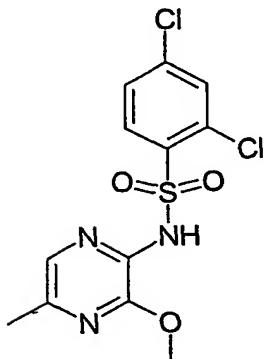
¹H NMR (D6-DMSO) δ 10.83 (1H, br s), 7.96 (2H, d), 7.65 (2H, d), 7.60 (1H, s), 3.88 (3H, s), 2.28 (3H, s)

MP 155-156°C

Example 47

2,4-Dichloro-*N*-(3-methoxy-5-methyl-2-pyrazinyl)benezenesulphonamide

5



Prepared by the method of Example 1 using 3-methoxy-5-methyl-2-pyrazinamine (0.1g) and 2,4-dichlorobenzenesulphonyl chloride (0.21g). Yield 0.041g.

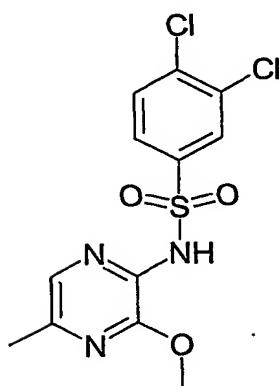
m/e 348 (M+1⁺, 100%)

10 ¹H NMR (D6-DMSO) δ 8.05 (1H, d), 7.83 (1H, d), 7.64 (1H, dd), 7.54 (1H, br s), 3.87 (3H, s), 2.27 (3H, s)

MP 135-136°C

Example 48

15 3,4-Dichloro-*N*-(3-methoxy-5-methyl-2-pyrazinyl)benezenesulphonamide



Prepared by the method of Example 1 using 3-methoxy-5-methyl-2-pyrazinamine (0.1g) and 3,4-dichlorobenzenesulphonyl chloride (0.21g). Yield 0.046g.

20 m/e 348 (M+1⁺, 100%)

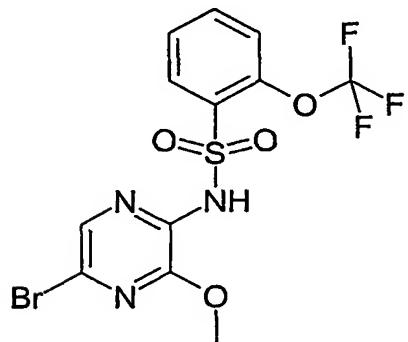
¹H NMR (D6-DMSO) δ 10.97 (1H, s), 8.14 (1H, d), 7.91 (1H, dd), 7.88 (1H, d), 7.63 (1H, s), 3.89 (3H, s), 2.27 (3H, s)

MP 148-149°C

Example 49

N-(5-Bromo-3-methoxy-2-pyrazinyl)-2-trifluoromethoxybenzenesulphonamide

5



Prepared by the method of Example 1 (reaction performed at room temperature) using 5-bromo-3-methoxy-2-pyrazinamine (0.1g) and 2-trifluoromethoxybenzenesulphonyl chloride (0.13g). Yield 0.097g

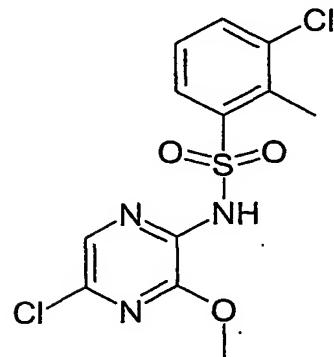
10 m/e 428 (M-1⁺, 100%)

¹H NMR (D6-DMSO) δ 8.03 (1H, dd), 7.87 (1H, s), 7.82-7.74 (1H, m), 7.60-7.52 (2H, m), 3.92 (3H, s)

MP 156-157°C

15 **Example 50**

3-Chloro-*N*-(5-chloro-3-methoxy-2-pyrazinyl)-2-methylbenzenesulphonamide



Prepared by the method of Example 1 (reaction performed at room temperature) using 5-chloro-3-methoxy-2-pyrazinamine (0.1g) and 3-chloro-2-methylbenzenesulphonyl chloride (0.15g). Yield 0.085g.

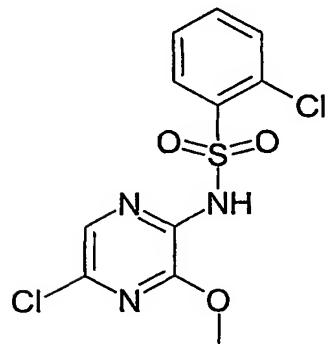
m/e 346 (M-1⁺, 100%)

¹H NMR (CDCl₃) δ 8.17 (1H, d), 7.69 (1H, br s), 7.64 (1H, s), 7.61 (2H, d), 7.30 (1H, t), 4.04 (3H, s), 2.73 (3H, s)

MP 150-152°C

5 **Example 51**

2-Chloro-N-(5-chloro-3-methoxy-2-pyrazinyl)benzenesulphonamide



Prepared by the method of Example 1 (reaction performed at room temperature) using 5-chloro-3-methoxy-2-pyrazinamine (0.1g) and 2-chlorobenzenesulphonyl chloride (0.13g).

10 Yield 0.082g.

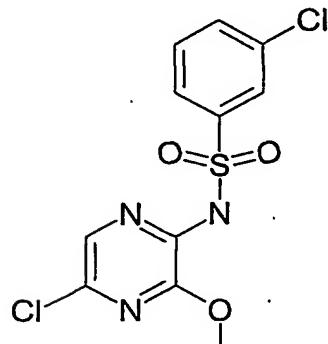
m/e 332 (M+1⁺, 100%)

¹H NMR (CDCl₃) δ 8.33 (1H, d), 7.82 (1H, s), 7.64-7.62 (1H, m), 7.61 (1H, s), 7.50-7.42 (2H, m), 4.04 (3H, s)

15 MP 190-192°C

Example 52

3-Chloro-N-(5-chloro-3-methoxy-2-pyrazinyl)benzenesulphonamide



Prepared by the method of Example 1 (reaction performed at room temperature) using 5-chloro-3-methoxy-2-pyrazinamine (0.1g) and 3-chlorobenzenesulphonyl chloride (0.13g).

Yield 0.095g.

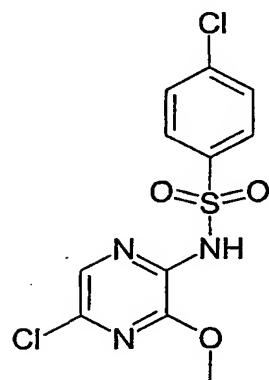
m/e 332 (M+1⁺, 100%)

5 ¹H NMR (CDCl₃) δ 8.14 (1H, s), 8.03 (1H, d), 7.76 (1H, s), 7.68-7.53 (2H, m), 7.46 (1H, t), 4.02 (3H, s)

MP 129-130°C

Example 53

10 4-Chloro-N-(5-chloro-3-methoxy-2-pyrazinyl)benzenesulphonamide



Prepared by the method of Example 1 (reaction performed at room temperature) using 5-chloro-3-methoxy-2-pyrazinamine (0.1g) and 4-chlorobenzenesulphonyl chloride (0.13g).

15 Yield 0.05g.

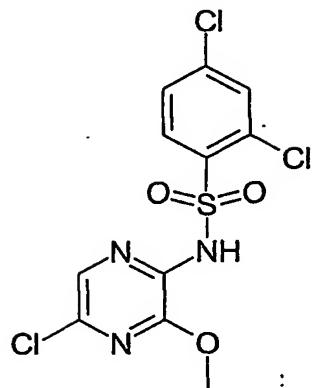
m/e 332 (M+1⁺, 100%)

¹H NMR (CDCl₃) δ 8.07 (2H, d), 7.75 (1H, s), 7.56 (1H, s), 7.49 (2H, d), 4.02 (3H, s)

MP 179-180°C

20 **Example 54**

N-(5-Chloro-3-methoxy-2-pyrazinyl)-2,4-dichlorobenzenesulphonamide



Prepared by the method of Example 1 (reaction performed at room temperature) using 5-chloro-3-methoxy-2-pyrazinamine (0.1g) and 2,4-dichlorobenzenesulphonyl chloride (0.13g). Yield 0.045g.

5 m/e 368 (M-1⁺, 100%)

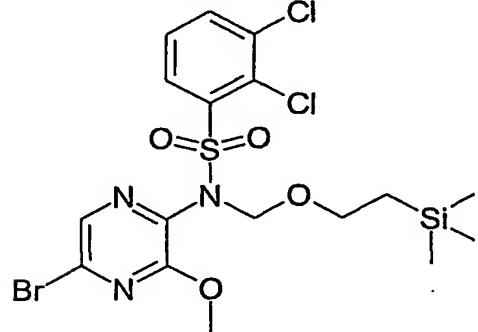
¹H NMR (CDCl₃) δ 8.27 (1H, d), 7.78 (1H, s), 7.63 (1H, s), 7.48 (1H, s), 7.43 (1H, d), 4.05 (3H, s)

MP 170-171°C

10 **Example 55**

2,3-Dichloro-N-[3-methoxy-5-(4-morpholinyl)-2-pyrazinyl]benzenesulphonamide

a) *N*-(5-Bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-*N*-{[2-(trimethylsilyl)ethoxy]methyl}benzenesulphonamide



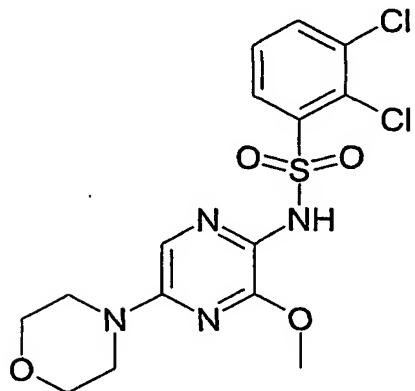
15

A mixture of *N*-(5-Bromo-3-methoxy-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide (Example 8) (0.40g), diisopropylethylamine (0.26g) and [2-(chloromethoxy)ethyl]trimethylsilane (0.25g) in dichloromethane (50mL) was stirred at room temperature. After 2h, the solution was washed with water, dried (MgSO₄) and 20 evaporated. Chromatography on silica gel eluting with ethyl acetate/iso hexane mixtures gave the title compound as a white solid (0.40g).

¹H NMR (CDCl₃) δ 8.09 (1H, s), 7.96 (1H, dd), 7.68 (1H, dd), 7.29 (1H, t), 5.24 (2H, s), 3.92 (3H, s), 3.77-3.73 (2H, m), 0.86-0.82 (2H, m), 0.00 (9H, s)

b) 2,3-Dichloro-N-[3-methoxy-5-(4-morpholinyl)-2-pyrazinyl]benzenesulphonamide

5



N-(5-Bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-*N*-(2-(trimethylsilyl)ethoxy)methylbenzenesulphonamide

(0.30g) and morpholine (0.45g) in acetonitrile (10mL) was heated at 50°C. After 16h, the 10 solution was evaporated. Chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound with SEM group attached, as a white solid. The solid was dissolved in trifluoroacetic acid (5.0mL) and dichloromethane (5.0mL). After 2h, the solution was evaporated. Chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound as a white solid (0.06g).

15 m/e 417 (M-1⁺, 100%)

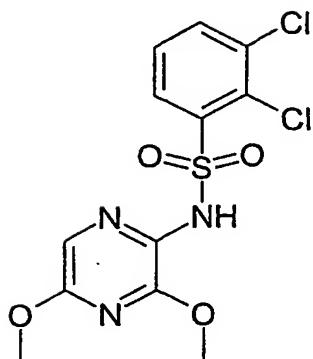
¹H NMR (CDCl₃) δ 8.17 (1H, d), 7.65 (1H, d), 7.41 (1H, s), 7.34 (1H, t), 7.16 (1H, s), 3.89 (3H, s), 3.80-3.75 (4H, m), 3.40-3.35 (4H, m)

MP 167-168°C

20

Example 56

2,3-Dichloro-N-[3,5-dimethoxy-2-pyrazinyl]benzenesulphonamide



5 *N*-(5-Bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-*N*-[{2-(trimethylsilyl)ethoxy}methyl]benzenesulphonamide (0.30g) in methanolic sodium methoxide (10mL of 0.5 molar solution) was stirred at room temperature. After 16h, the solution was evaporated to dryness and dichloromethane (10mL) and trifluoroacetic acid (10mL) added. After 2h, the mixture was evaporated to dryness, dichloromethane added and the inorganic salts removed by filtration. Chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound as a white solid (0.1g).

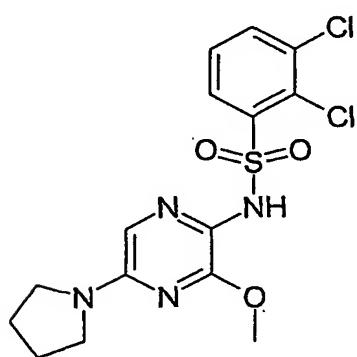
10 m/e 364 (M+1⁺, 100%)

10 ¹H NMR (CDCl₃) δ 8.21 (1H, d), 7.67 (1H, d), 7.50 (1H, s), 7.37 (1H, t), 7.26 (1H, s), 3.98 (3H, s), 3.87 (3H, s)

MP 138-139°C

15 **Example 57**

2,3-Dichloro-*N*-[3-methoxy-5-(1-pyrrolinyl)-2-pyrazinyl]benzenesulphonamide

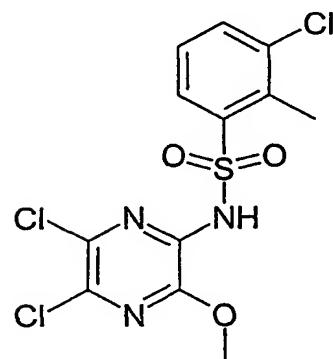


20 Prepared by the method of Example 55 using pyrrolidine (0.4g) and *N*-(5-bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-*N*-[{2-(trimethylsilyl)ethoxy}methyl]benzenesulphonamide (0.3g). Yield 0.045g.
m/e 403 (M+1⁺, 100%)

¹H NMR (CDCl₃) δ 8.08 (1H, d), 7.64 (1H, d), 7.30 (1H, t), 7.21 (1H, s), 6.99 (1H, s), 3.81 (3H, s), 3.40-3.35 (4H, m), 2.00-1.95 (4H, m)
 MP 179-180°C

5 **Example 58**

3-Chloro-N-(5,6-dichloro-3-methoxy-2-pyrazinyl)-2-methylbenzenesulphonamide



Prepared by the method of Example 1 (reaction performed at room temperature) using 5,6-dichloro-3-methoxy-2-pyrazinamine (0.1g) and 3-chloro-2-methylbenzenesulphonyl chloride (0.14g). Yield 0.13g.

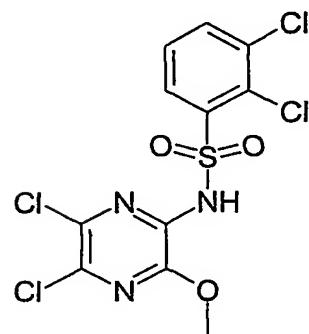
m/e 381 (M-1⁺, 100%)

¹H NMR (CDCl₃) δ 8.25 (1H, d), 7.65 (1H, br s), 7.62 (1H, d), 7.35 (1H, t), 4.04 (3H, s), 2.73 (3H, s)

MP 177-178°C

Example 59

2,3-Dichloro-N-(5,6-dichloro-3-methoxy-2-pyrazinyl)benzenesulphonamide



20 Prepared by the method of Example 1 (reaction performed at room temperature) using 5,6-dichloro-3-methoxy-2-pyrazinamine (0.1g) and 2,3-dichlorobenzenesulphonyl chloride (0.15g). Yield 0.12g.

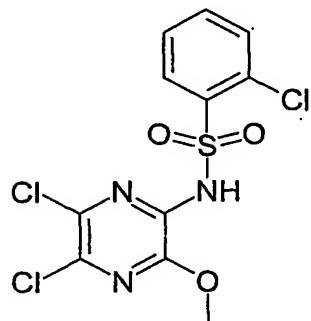
m/e 402 (M-1⁺, 100%)

¹H NMR (CDCl₃) δ 8.31 (1H, d), 7.81 (1H, br s), 7.72 (1H, d), 7.45 (1H, t), 4.05 (3H, s)

MP 172-173°C

5 **Example 60**

2-Chloro-N-(5,6-dichloro-3-methoxy-2-pyrazinyl)benzenesulphonamide



Prepared by the method of Example 1 (reaction performed at room temperature) using 5,6-dichloro-3-methoxy-2-pyrazinamine (0.1g) and 2-chlorobenzenesulphonyl chloride (0.13g). Yield 0.096g.

m/e 367 (M-1⁺, 100%)

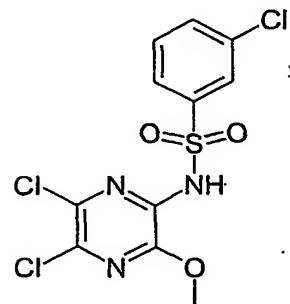
¹H NMR (CDCl₃) δ 8.39 (1H, d), 7.79 (1H, br s), 7.58-7.45 (3H, m), 4.04 (3H, s)

MP 217-218°C

15

Example 61

3-Chloro-N-(5,6-dichloro-3-methoxy-2-pyrazinyl)benzenesulphonamide



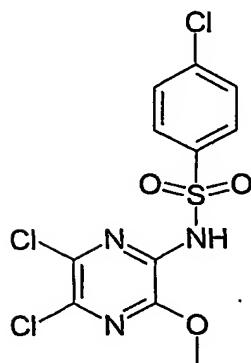
20 Prepared by the method of Example 1 (reaction performed at room temperature) using 5,6-dichloro-3-methoxy-2-pyrazinamine (0.1g) and 3-chlorobenzenesulphonyl chloride (0.13g). Yield 0.047g.

m/e 367 (M-1⁺, 100%)

¹H NMR (CDCl₃) δ 8.19 (1H, s), 8.07 (1H, d), 7.61 (1H, d), 7.59 (1H, br s), 7.50 (1H, t), 4.02 (3H, s)
 MP 171-172°C

5 **Example 62**

4-Chloro-N-(5,6-dichloro-3-methoxy-2-pyrazinyl)benzenesulphonamide



Prepared by the method of Example 1 (reaction performed at room temperature) using 5,6-dichloro-3-methoxy-2-pyrazinamine (0.1g) and 4-chlorobenzenesulphonyl chloride (0.13g). Yield 0.09g.

m/e 367 (M-1⁺, 100%)

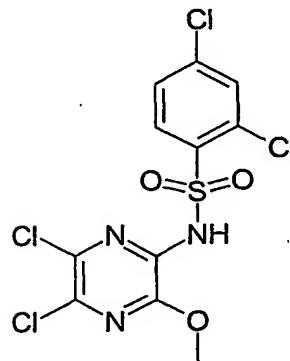
¹H NMR (CDCl₃) δ 8.11 (2H, d), 7.57 (1H, br s), 7.50 (2H, d), 4.02 (3H, s)

MP 186-187°C

15

Example 63

2,4-Dichloro-N-(5,6-dichloro-3-methoxy-2-pyrazinyl)benzenesulphonamide



20 Prepared by the method of Example 1 (reaction performed at room temperature) using 5,6-dichloro-3-methoxy-2-pyrazinamine (0.1g) and 2,4-dichlorobenzenesulphonyl chloride (0.15g). Yield 0.076g.

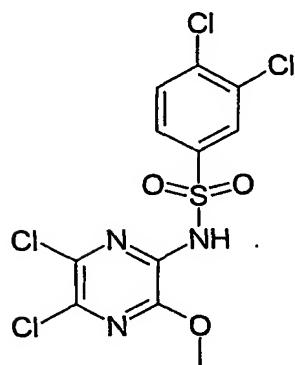
m/e 402 (M-1⁺, 100%)

¹H NMR (CDCl₃) δ 8.30 (1H, d), 7.76 (1H, br s), 7.50 (1H, s), 7.48 (1H, d), 4.05 (3H, s)

MP 171-172°C

5 **Example 64**

3,4-Dichloro-N-(5,6-dichloro-3-methoxy-2-pyrazinyl)benzenesulphonamide



Prepared by the method of Example 1 (reaction performed at room temperature) using 5,6-dichloro-3-methoxy-2-pyrazinamine (0.1g) and 3,4-dichlorobenzenesulphonyl chloride (0.15g). Yield 0.11g.

m/e 402 (M-1⁺, 100%)

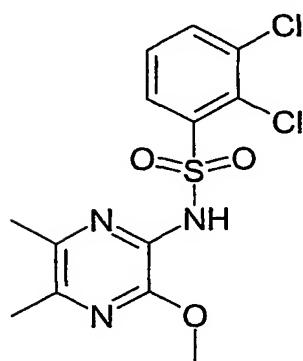
¹H NMR (CDCl₃) δ 8.30 (1H, s), 8.01 (1H, d), 7.63 (1H, d), 7.58 (1H, br s), 4.03 (3H, s)

MP 189-191°C

15

Example 65

2,3-Dichloro-N-(3-methoxy-5,6-dimethyl-2-pyrazinyl)benzenesulphonamide



20 Prepared by the method of Example 1 using 3-methoxy-5,6-dimethyl-2-pyrazinamine (0.07g) and 2,3-dichlorobenzenesulphonyl chloride (0.12g). Yield 0.04g.

m/e 360 (M-1⁺, 100%)

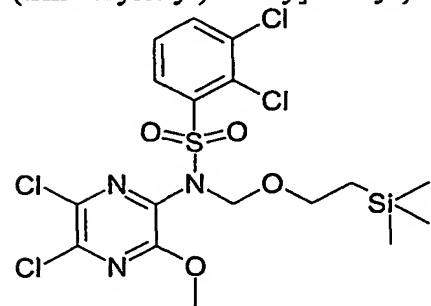
¹H NMR (CDCl₃) δ 8.32 (1H, d), 7.67 (1H, s), 7.65 (1H, d), 7.39 (1H, t), 3.95 (3H, s), 2.28 (3H, s), 2.14 (3H, s)

MP 165-166°C

5 **Example 66**

2,3-Dichloro-N-(6-chloro-3,5-dimethoxy-2-pyrazinyl)benzenesulphonamide

a) 2,3-Dichloro-N-(5,6-dichloro-3-methoxy-2-pyrazinyl)-N-[(2-(trimethylsilyl)ethoxy)methyl]benzenesulphonamide



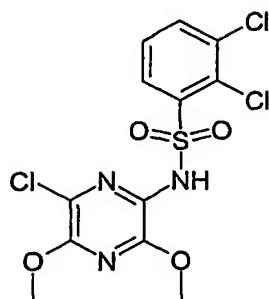
10

To a stirred solution of 2,3-Dichloro-N-(5,6-dichloro-3-methoxy-2-pyrazinyl)benzenesulphonamide (0.68g) in dichloromethane (20mL) was added triethylamine (0.491mL) followed by 2-(trimethylsilyl)ethoxymethyl chloride (0.328g) and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water (50mL) and extracted into ethyl acetate (3x20mL). The combined extracts were dried (MgSO₄), filtered and concentrated. Chromatography on silica gel eluting with ethyl acetate/iso hexane mixtures gave the sub-title compound as a white solid (0.74g).

20 ¹H NMR (CDCl₃) δ 8.02 (1H, dd), 7.70 (1H, dd), 7.34 (1H, t), 5.22 (2H, s), 3.96 (3H, s), 3.73 (2H, dd), 0.91-0.79 (2H, m), -0.03 (9H, s)

b) 2,3-Dichloro-N-(6-chloro-3,5-dimethoxy-2-pyrazinyl)benzenesulphonamide

25



2,3-Dichloro-N-(5,6-dichloro-3-methoxy-2-pyrazinyl)-N-[(2-trimethylsilyl)ethoxy]methylbenzenesulfonamide (0.10g) was dissolved in methanol (1.0mL) and a solution of sodium methoxide in methanol (0.1mL of a 25% solution in methanol) was added. The reaction was stirred at room temperature for 30 min and was concentrated. The residue was dissolved in trifluoroacetic acid (2.0mL) and was stirred at room temperature for 30 min. The reaction mixture was concentrated and chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound as a white solid (0.028g).

m/e 397 (M-1⁺, 100%)

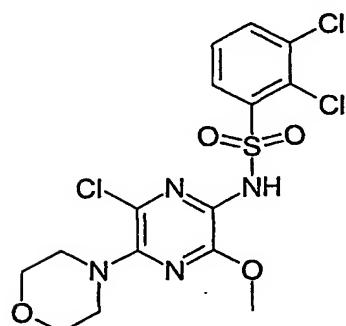
¹H NMR (CDCl₃) δ 8.26 (1H, d), 7.69 (1H, d), 7.41 (1H, t), 7.41 (1H, br s), 4.02 (3H, s), 3.91 (3H, s)

MP 163-165°C

15

Example 67

2,3-Dichloro-N-[6-chloro-3-methoxy-5-(4-morpholinyl)-2-pyrazinyl]benzenesulphonamide



20

2,3-Dichloro-N-(5,6-dichloro-3-methoxy-2-pyrazinyl)-N-[(2-trimethylsilyl)ethoxy]methylbenzenesulphonamide (Example 66 part a) (0.10 g) was dissolved in THF (1.0mL) and a solution of morpholine (0.05g) in THF (0.1mL) was added. The reaction was stirred at room temperature for 30 min and was concentrated.

The residue was dissolved in trifluoroacetic acid (2.0mL) and dichloromethane (2.0mL) and was stirred at room temperature for 30 min. The reaction mixture was concentrated and chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound as a white solid (0.042g).

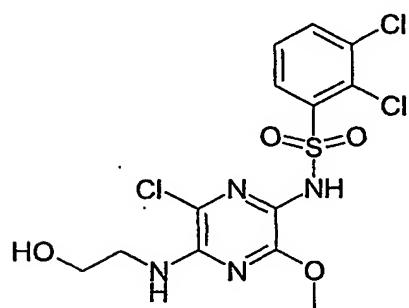
5 m/e 452 (M-1⁺, 100%)

¹H NMR (CDCl₃) δ 8.28 (1H, dd), 7.69 (1H, dd), 7.49 (1H, br s), 7.43 (1H, t), 3.96 (3H, s), 3.79 (4H, dd), 3.28 (4H, dd)

MP 150-151°C

10 **Example 68**

2,3-Dichloro-N-[6-chloro-5-(2-hydroxyethylamino)-3-methoxy-2-pyrazinyl]benzenesulphonamide



15

Prepared by the method of Example 67 using 2-aminoethanol (0.05g) and 2,3-dichloro-N-(5,6-dichloro-3-methoxy-2-pyrazinyl)-N-{{[2-(trimethylsilyl)ethoxy]methyl}benzenesulfonamide (0.1g). Yield 0.015g.

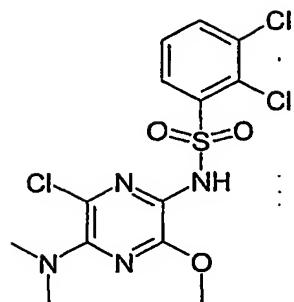
m/e 426 (M-1⁺, 100%)

20 ¹H NMR (D6-DMSO) δ 10.31 (1H, s), 7.91 (2H, dd), 7.52 (1H, t), 6.89 (1H, br s), 4.71 (1H, t), 3.63 (3H, s), 3.53 (2H, dd), 3.40 (2H, dd)

Example 69

2,3-Dichloro-N-[6-chloro-5-dimethylamino-3-methoxy-2-pyrazinyl]benzenesulphonamide

25



Prepared by the method of Example 67 using dimethylamine (5mL of a 2M solution in tetrahydrofuran) and 2,3-dichloro-N-(5,6-dichloro-3-methoxy-2-pyrazinyl)-N-[(2-(trimethylsilyl)ethoxy)methyl]benzenesulfonamide (0.1g). Yield 0.015g.

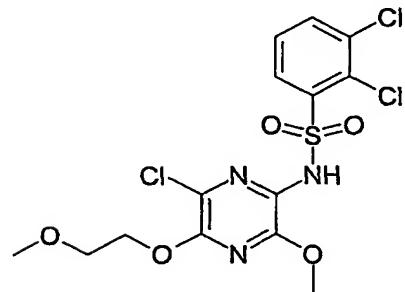
5 m/e 410 (M-1⁺, 100%)

¹H NMR (D₆-DMSO) δ 7.99-7.93 (2H, m), 7.56 (1H, t), 3.74 (3H, s), 2.99 (6H, s)

MP 145-146°C

Example 70

10 2,3-Dichloro-N-[6-chloro-3-methoxy-5-(2-methoxyethoxy)-2-pyrazinyl]benzenesulphonamide



Sodium hydride (0.019g of 60% dispersion in oil) was added to a solution of 2,3-dichloro-15 N-(5,6-dichloro-3-methoxy-2-pyrazinyl)-N-[(2-(trimethylsilyl)ethoxy)methyl]benzenesulfonamide (0.25g) in 2-methoxyethanol (3.0mL) at room temperature. After 16h, the solvent was evaporated and trifluoroacetic acid (2.0mL) added. After 1h, the reaction mixture was concentrated and chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound as a white 20 solid (0.08g).

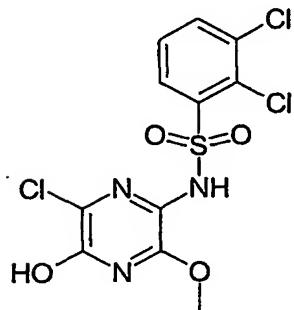
m/e 442 (M+1⁺, 100%)

¹H NMR (CDCl₃) δ 8.24 (1H, dd), 7.70 (1H, dd), 7.41 (1H, t), 4.50-4.40 (2H, m), 3.96 (3H, s), 3.80-3.70 (2H, m), 3.42 (3H, s)

MP 193-194°C

Example 71

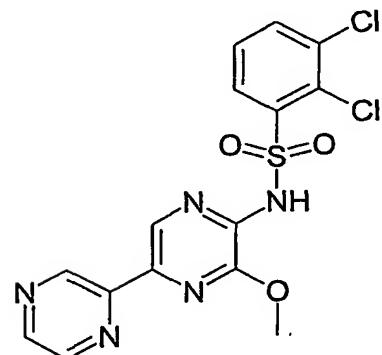
2,3-Dichloro-N-[6-chloro-5-hydroxy-3-methoxy-2-pyrazinyl]benzenesulphonamide



5 tetrabutylammonium hydroxide (0.28g of 40% aqueous solution) was added to a solution of 2,3-dichloro-N-(5,6-dichloro-3-methoxy-2-pyrazinyl)-N-[(2-
 10 trimethylsilyl)ethoxy]methyl}benzenesulfonamide (0.25g) in 1,2-dimethoxyethane (3.0mL) at room temperature. After 16h, the solution was diluted with ethyl acetate (20mL). The organic solution was washed with aqueous citric acid (10mL) and brine, dried (MgSO₄) and evaporated. Chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound containing the SEM group, as a white solid (0.08g). The solid was dissolved in trifluoroacetic acid (2.0mL) and dichloromethane (2.0mL) and stirred at room temperature for 1h. The reaction mixture was concentrated and chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound as a white solid (0.027g).

15 m/e 384 (M+1⁺, 100%)1H NMR (CDCl₃) δ 12.56 (1H, s), 10.87 (1H, s), 7.96 (2H, t), 7.56 (1H, t), 3.74 (3H, s)**Example 72**

20 2,3-Dichloro-N-[6-methoxy-5-([2,2']bipyrazinyl)]benzenesulphonamide



5 *N*-(5-Bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-*N*-[{2-(trimethylsilyl)ethoxy}methyl]benzenesulphonamide (Example 55 part a) (0.70g), tetrakis(triphenylphosphine)palladium(0) (0.1g) and 2-(tributylstannanyl)pyrazine (0.50g) in toluene (20mL) was heated under nitrogen at 100°C. After 16h, chromatography on silica gel eluting with ethyl acetate/iso hexane mixtures gave the title compound protected with the SEM group as a white solid. The solid was dissolved in trifluoroacetic acid (2.0mL) and dichloromethane (2.0mL) and stirred at room temperature for 1h. The reaction mixture was concentrated, toluene added and evaporated. The title compound crystallised from acetonitrile to give a white solid (0.38g).

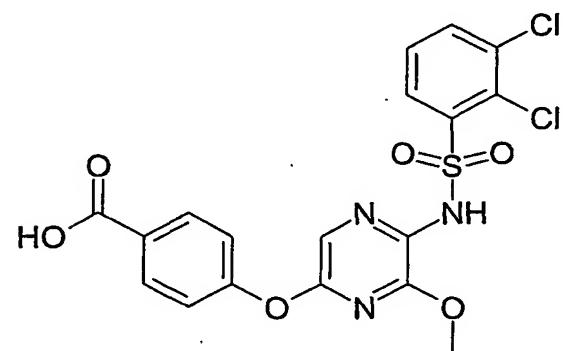
10 m/e 410 (M-1⁺, 100%)

¹H NMR (D6 DMSO) δ 9.35 (1H, s), 8.69 (1H, d), 8.67 (1H, d), 8.40 (1H, br s), 8.14 (1H, d), 7.96 (1H, d), 7.61 (1H, t), 4.07 (3H, s)

MP 199-200°C

15 **Example 73**

4-[5-(2,3-Dichlorobenzenesulphonylamino)-6-methoxy-2-pyrazinyl]benzoic acid



20 4-Hydroxybenzoic acid *tert* butyl ester (0.13g), *N*-(5-bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-*N*-[{2-(trimethylsilyl)ethoxy}methyl]benzenesulphonamide (Example 55 part a) (0.35g) and caesium carbonate (0.42g) in acetonitrile (10mL) was heated at 50°C. After 12h, the mixture was diluted with ethyl acetate, washed with water, dried (MgSO₄) and evaporated. Chromatography on silica gel eluting with ethyl acetate/iso hexane mixtures gave the title compound protected with the SEM group and *tert* butyl group as an oil. The oil was dissolved in trifluoroacetic acid (2.0mL) and stirred at room temperature for 3h. The reaction mixture was concentrated, toluene added and evaporated to give the title compound as a white solid (0.19g).

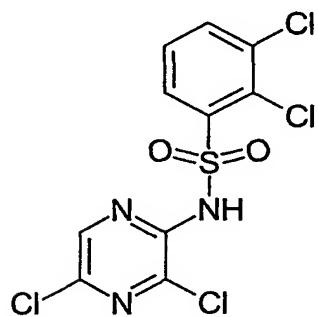
25 m/e 468 (M-1⁺, 100%)

¹H NMR (CDCl₃) δ 8.28 (1H, d), 8.11 (2H, d), 7.80 (1H, br s), 7.71 (1H, d), 7.45 (2H, m), 7.12 (2H, d), 3.89 (3H, s)

MP 186-187°C

5 **Example 74**

2,3-Dichloro-N-(3,5-dichloro-2-pyrazinyl)benzenesulphonamide



10 Prepared by the method of Example 1 (reaction performed at room temperature) using 3,5-dichloro-2-pyrazinamine (2.0g) and 2,3-dichloro benzenesulphonyl chloride (2.94g). Yield 3.0g.

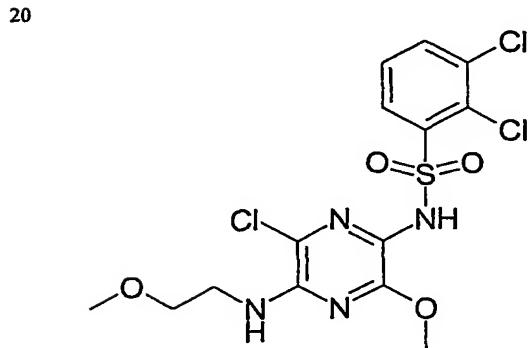
m/e 372 (M-1⁺, 100%)

¹H NMR (D6 DMSO) δ 8.29 (1H, s), 8.06 (1H, dd), 7.94 (1H, dd), 7.57 (1H, t)

15 MP 181-182°C

Example 75

2,3-Dichloro-N-{6-chloro-3-methoxy-5-[(2-methoxyethyl)amino]-2-pyrazinyl}benzenesulphonamide



20 Prepared by the method of Example 67 using 2-methoxyethylamine (3mL) and 2,3-dichloro-N-(5,6-dichloro-3-methoxy-2-pyrazinyl)-N-[(2-trimethylsilyl)ethoxy]methylbenzenesulphonamide (0.24g). Yield 0.08g.

m/e 439 ($M+1^+$, 100%)

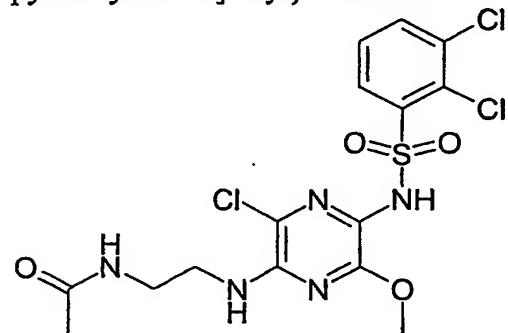
^1H NMR (D6-DMSO) δ 10.33 (1H, s), 7.92 (2H, dd), 7.52 (1H, t), 7.00 (1H, s), 3.64 (3H, s), 3.47 (4H, s), 3.24 (2H, dd)

MP 177-178°C

5

Example 76

N-{2-[3-Chloro-5-(2,3-dichlorobenzenesulphonylamino)-6-methoxy-2-pyrazinylamino]ethyl}acetamide



10

2,3-Dichloro-*N*-(5,6-dichloro-3-methoxy-2-pyrazinyl)-*N*-{[2-(trimethylsilyl)ethoxy]methyl}benzenesulphonamide (Example 66 part a) (0.26g) was dissolved in acetonitrile (1.0mL) and *N*-acetylenediamine (0.055mL) and triethylamine (0.19mL) added. After 48h, the reaction mixture was concentrated and chromatography on silica gel eluting with ethyl acetate gave the title compound protected with the SEM group, as an oil (0.13g). The oil was dissolved in dichloromethane (2.0mL) and boron trifluoride etherate (0.14ml) added. After 2h, ethyl acetate (20mL) was added and the mixture washed with 5% aqueous citric acid (5mL), dried (MgSO_4) and evaporated. Chromatography on silica gel eluting with ethyl acetate gave the title compound as a solid (0.031g).

20

m/e 470 ($M+1^+$, 100%)

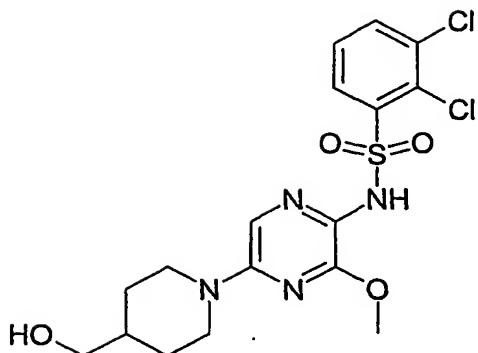
^1H NMR (D6-DMSO) δ 10.32 (1H, s), 7.93-7.88 (2H, m), 7.52 (1H, t), 7.10 (1H, s), 3.65 (3H, s), 3.40-3.10 (4H, m), 1.75 (3H, s)

MP 150-152°C

25

Example 77

2,3-Dichloro-*N*-[5-(4-hydroxymethyl-1-piperidinyl)-3-methoxy-2-pyrazinyl]benzenesulphonamide



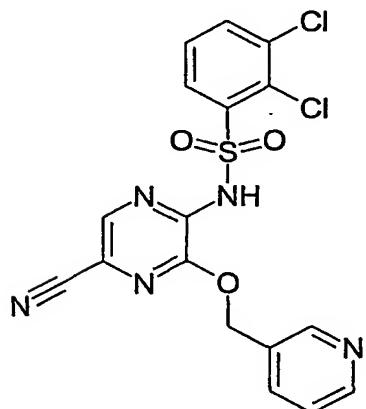
Prepared by the method of Example 55 using 4-(hydroxymethyl)piperidine (0.4g) and *N*-(5-bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-*N*-[2-(trimethylsilanyl)ethoxy]methylbenzenesulphonamide (0.3g). Yield 0.012g.

5 m/e 447 ($M+1^+$, 100%)

¹H NMR ($CDCl_3$) δ 8.14 (1H, dd), 7.65 (1H, dd), 7.33 (1H, t), 7.20 (1H, s), 4.20 - 4.10 (2H, m), 3.86 (3H, s), 3.60-3.50 (2H, m), 2.90-2.70 (2H, m), 1.90-1.70 (3H, m), 1.40-1.20 (3H, m)

10 **Example 78**

2,3-Dichloro-*N*-(5-cyano-3-(3-pyridinylmethoxy)-2-pyrazinyl)benzenesulphonamide



N-(5-Bromo-3-(3-pyridinylmethoxy)-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide

15 (Example 34) (0.15g), tetrakis(triphenylphosphine)palladium(0) (0.04g) and zinc cyanide (0.03g) in *N,N*-dimethylformamide (5.0mL) was heated at 70°C. After 5h, the mixture was diluted with ethyl acetate (30mL) and washed with 5% aqueous citric acid (5mL), dried ($MgSO_4$) and evaporated. Chromatography on silica gel eluting with ethyl acetate/isohexane mixtures containing 1% acetic acid gave the title compound as a white solid (0.058g).

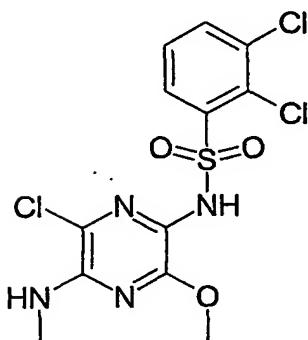
20 m/e 436 ($M+1^+$, 100%)

¹H NMR (D6 DMSO) δ 8.70 -7.65 (2H, m), 8.29 (1H, dd), 7.99 (1H, s), 7.78 (1H, d), 7.73 (1H, dd), 7.46 (1H, t), 7.40-7.35 (1H, m), 5.45 (2H, s)

MP 222-224°C

5 **Example 79**

2,3-Dichloro-N-(6-chloro-3-methoxy-5-methylamino-2-pyrazinyl)benzenesulphonamide



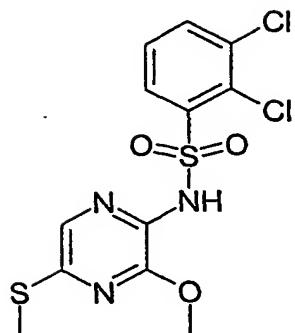
10 3-Dichloro-N-(5,6-dichloro-3-methoxy-2-pyrazinyl)-N-[(2-(trimethylsilyl)ethoxy]methyl}benzenesulphonamide (Example 66 part a) (0.25 g) was dissolved in methanol (1.0mL) and methylamine (2.0mL of 40% aqueous solution) was added. After 16h, the solution was partitioned between water and ethyl acetate. The organic layer was dried (MgSO₄) and evaporated. The residue was dissolved in dichloromethane (2.0 mL) and boron trifluoride etherate (0.25mL) added. After 1h, ethyl acetate (20mL) was added and the solution washed with 5% aqueous citric acid (5mL), dried (MgSO₄) and evaporated. Chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound as a white solid (0.05g).
 m/e 395 (M+1⁺, 100%)

15 ¹H NMR (D6-DMSO) δ 10.27 (1H, s), 7.95-7.87 (2H, m), 7.51 (1H, dd), 7.10-7.00 (1H, m), 3.64 (3H, s), 2.84 (3H, s)

20 MP 185-186°C

Example 80

2,3-Dichloro-N-(3-methoxy-5-methylsulphonyl-2-pyrazinyl)benzenesulphonamide



N-(5-Bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-*N*-{(2-(trimethylsilyl)ethoxy)methyl}benzenesulphonamide

(0.30g) and sodium thiomethoxide (0.05g) in acetonitrile (10mL) was stirred at room temperature. After 2h, the solution was evaporated. Chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound with SEM group attached. The compound was dissolved in trifluoroacetic acid (5mL). After 2h, toluene (20mL) was added and the solution evaporated. Chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound as a white solid (0.16g).

10 m/e 380 (M+1⁺, 100%)

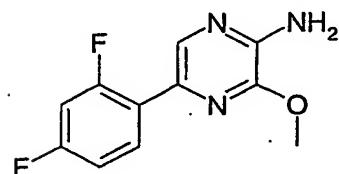
¹H NMR (CDCl₃) δ 8.25 (1H, d), 7.70 (1H, s), 7.68 (1H, d), 7.52 (1H, s), 7.39 (1H, t), 4.03 (3H, s), 2.48 (3H, s)

MP 141-142°C

15 **Example 81**

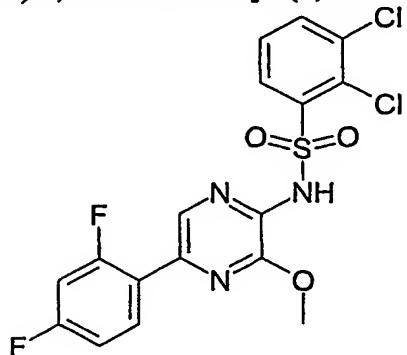
2,3-Dichloro-*N*-[5-(2,4-difluorophenyl)-3-methoxy-2-pyrazinyl]benzenesulphonamide

a) 5-(2,4-difluorophenyl)-3-methoxy-2-pyrazinamine



20

5-Bromo-3-methoxy-2-pyrazinamine (0.3g), cesium fluoride (0.8g), 2,4-difluorobenzeneboronic acid (0.4g) and [1,1'-bis(diphenylphosphino)ferrocene]palladium (II) chloride (0.04g) in methanol (20mL) was heated at 70°C. After 6h, the solvent was evaporated and the residue purified by chromatography on silica eluting with ethyl acetate/isohexane mixtures to give the sub-title compound (0.2g).

b) 2,3-Dichloro-*N*-[5-(2,4-difluorophenyl)-3-methoxy-2-pyrazinyl]benzenesulphonamide

Prepared by the method of Example 1 using 5-(2,4-difluorophenyl)-3-methoxy-2-

5 pyrazinamine (0.2g) and 2,3-dichlorobenzenesulphonyl chloride (0.2g). Yield 0.06g.
m/e 444 (M-1⁺, 100%)

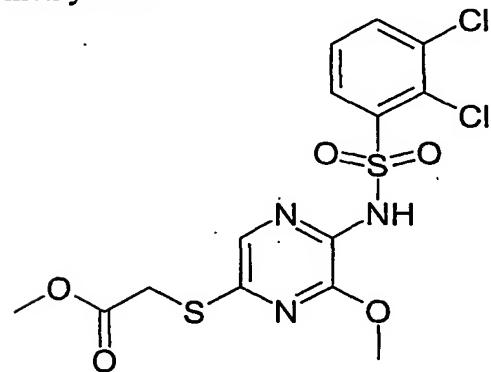
¹H NMR (D6-DMSO) δ 8.15 (1H, d), 8.05 - 7.95 (2H, m), 7.93 (1H, d), 7.60 (1H, t), 7.45-
7.35 (1H, m), 7.30-7.20 (1H, m), 4.03 (3H, s)

MP 169-170°C

10

Example 82

[5-(2,3-Dichlorobenzenesulphonylamino)-6-methoxy-2-pyrazinylsulphonyl]acetic acid
methyl ester



15 *N*-(5-Bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-*N*-(2-(trimethylsilyl)ethoxy)methylbenzenesulphonamide
(0.40g), mercaptoacetic acid methyl ester (0.1g) and caesium carbonate (0.6g) in
acetonitrile (10mL) was stirred at room temperature. After 16h, the solution was diluted
with dichloromethane, filtered and evaporated. Chromatography on silica gel eluting with
20 ethyl acetate/isohexane mixtures gave the title compound with SEM group attached. The
compound was dissolved in trifluoroacetic acid (5mL). After 2h, toluene (20mL) was

added and the solution evaporated. Chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound as a white solid (0.15g).

m/e 438 (M+1⁺, 100%)

¹H NMR (CDCl₃) δ 8.26 (1H, dd), 7.73 (1H, s), 7.68 (1H, dd), 7.59 (1H, s), 7.41 (1H, t),

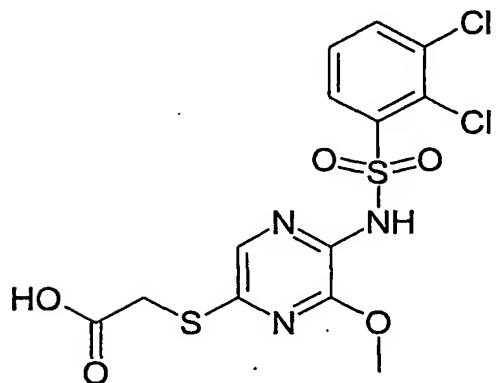
5 3.99 (3H, s), 3.80 (2H, s), 3.71 (3H, s)

MP 152-153°C

Example 83

[5-(2,3-Dichlorobenzenesulphonylamino)-6-methoxy-2-pyrazinylsulphanyl]acetic acid

10



[5-(2,3-Dichlorobenzenesulphonylamino)-6-methoxy-2-pyrazinylsulphanyl]acetic acid methyl ester (Example 82) (0.1g) and lithium hydroxide (0.04g) in methanol (5mL) and water (1mL) was stirred at room temperature. After 2h, the mixture was evaporated and saturated aqueous citric acid (5mL) added. The white solid was collected, washed with water and dried. Yield 0.07g.

15 m/e 424 (M+1⁺, 100%)

¹H NMR (CDCl₃) δ 8.27 (1H, dd), 7.90 (1H, br s), 7.70 (1H, dd), 7.61 (1H, s), 7.40 (1H, t),

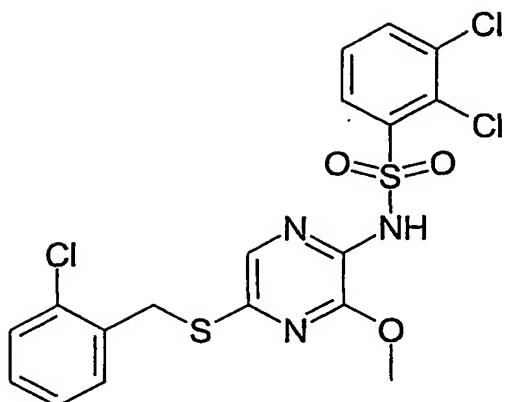
20 3.98 (3H, s), 3.80 (2H, s)

MP 138-140°C

Example 84

2,3-Dichloro-N-[5-(2-chlorobenzylsulphanyl)-3-methoxy-2-pyrazinyl]benzenesulphonamide

25



Prepared by the method of Example 82 using 2-chlorobenzylmercaptan (0.15g) and *N*-(5-bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-*N*-[{2-

5 (trimethylsilyl)ethoxy}methyl]benzenesulphonamide (0.4g). Yield 0.18g.
m/e 492 (M+1⁺, 100%)

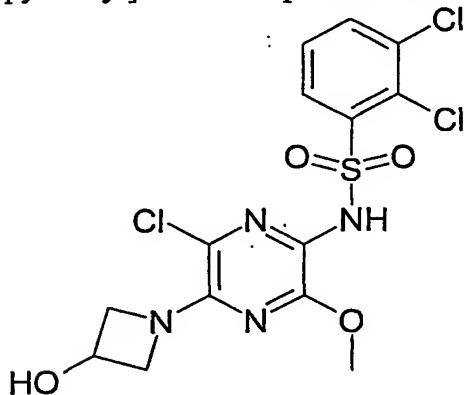
¹H NMR (CDCl₃) δ 8.26 (1H, dd), 7.73 (1H, s), 7.69 (1H, dd), 7.53 (1H, s), 7.40-7.30 (3H, m), 7.20-7.10 (2H, m), 4.39 (2H, s), 4.02 (3H, s)

MP 119-120°C

10

Example 85

2,3-Dichloro-*N*-(6-chloro-5-(3-hydroxy-1-azetidinyl)-3-methoxy-2-pyrazinyl)benzenesulphonamide



15 2,3-Dichloro-*N*-(5,6-dichloro-3-methoxy-2-pyrazinyl)-*N*-[{2-(trimethylsilyl)ethoxy}methyl]benzenesulphonamide (Example 66 part a) (0.20 g), azetidin-3-ol hydrochloride (0.082g) and triethylamine (0.25mL) in acetonitrile (3mL) and water (0.5mL) was stirred at room temperature. After 2h, the mixture was evaporated and triturated with diethyl ether. The ethereal solution was evaporated and the residue
20 dissolved in a 1molar solution of tetrabutylammonium fluoride in THF (6mL). After 16h,

the reaction mixture was concentrated and chromatography on silica gel eluting with ethyl acetate/isohexane mixtures gave the title compound as a white solid (0.024g).

m/e 442 (M+1⁺, 100%)

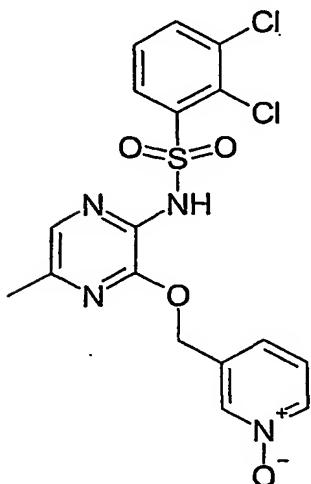
¹H NMR (D6-DMSO) δ 10.58 (1H, s), 7.92 (2H, d), 7.54 (1H, t), 5.66 (1H, s), 4.49 (1H, s), 4.36 (2H, t), 3.88 (2H, m), 3.67 (3H, s)

MP 93-95°C

Example 86

2,3-Dichloro-N-[5-methyl-3-(1-oxy-3-pyrazinylmethoxy)-2-

¹⁰ pyrazinyl]benzenesulphonamide



2,3-Dichloro-N-[5-methyl-3-(3-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide

(Example 24) (0.2g) and 3-chloroperbenzoic acid (0.35g) in dichloromethane (4mL) was

¹⁵ stirred at room temperature. After 0.5h, chromatography on silica gel eluting with 5% methanol in ethyl acetate containing 1% acetic acid gave the title compound as a white solid (0.16g).

m/e 441 (M+1⁺, 100%)

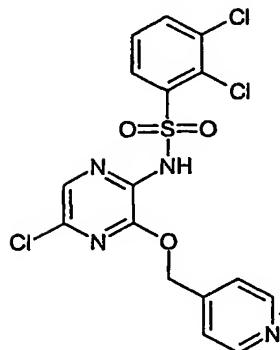
¹H NMR (D6-DMSO) δ 11.56 (1H, br s), 8.60 (1H, br s), 8.18 (1H, dt), 8.06 (1H, dd), 7.90

²⁰ (1H, dd), 7.61 (1H, br s), 7.56 (1H, t), 7.50-7.40 (2H, m), 5.36 (2H, s), 2.28 (3H, s)

MP 223-228°C

Example 87

2,3-Dichloro-N-[5-chloro-3-(4-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide



Prepared by the method of Example 31b using pyridine-4-methanol (0.4g) and 2,3-dichloro-N-(3,5-dichloro-2-pyrazinyl)benzenesulphonamide (Example 74) (0.4g). Yield 0.47g.

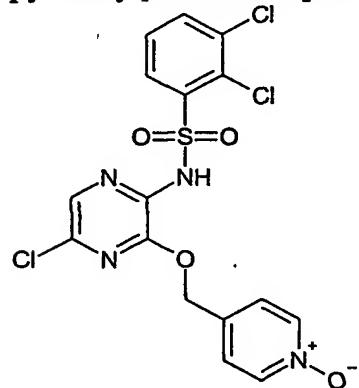
5 m/e 445 ($M+1^+$, 100%)

^1H NMR (D6-DMSO) δ 8.63 (2H, d), 8.08 (1H, dd), 7.91 (1H, dd), 7.83 (1H, s), 7.60 (2H, d), 7.55 (1H, t), 5.47 (2H, s)

MP 226-229°C decomposes

10 **Example 88**

2,3-Dichloro-N-[5-chloro-3-(1-oxy-4-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide



Prepared by the method of Example 86 using 2,3-dichloro-N-[5-chloro-3-(4-

15 pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide (Example 87) (0.1g). Yield 0.4g.
m/e 462 ($M+1^+$, 100%)

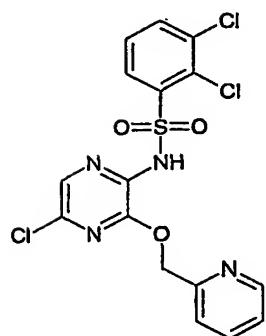
^1H NMR (D6-DMSO) δ 8.27 (2H, dt), 8.07 (1H, dd), 7.92 (1H, dd), 7.85 (1H, s), 7.60 (2H, d), 7.57 (1H, t), 5.38 (2H, s)

MP 208-211°C decomposes

20

Example 89

2,3-Dichloro-N-[5-chloro-3-(2-pyridinylmethoxy)-2-pyrazinyl]



Prepared by the method of Example 31b using pyridine-2-methanol (0.2g) and 2,3-dichloro-N-(3,5-dichloro-2-pyrazinyl)benzenesulphonamide (Example 74) (0.2g). Yield 0.1g.

m/e 445 ($M+1^+$, 100%)

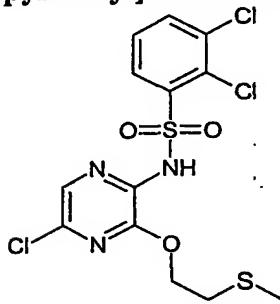
1H NMR (D6-DMSO) δ 8.58 (1H, dt), 8.08 (1H, dd), 7.92 (1H, dd), 7.80-7.90 (2H, m), 7.64 (1H, d), 7.56 (1H, t), 7.18-7.20 (1H, m), 5.47 (2H, s)

MP 147-148°C

10

Example 90

2,3-Dichloro-N-[5-chloro-3-(2-methylsulphanyloxy)-2-pyrazinyl]benzenesulphonamide



15

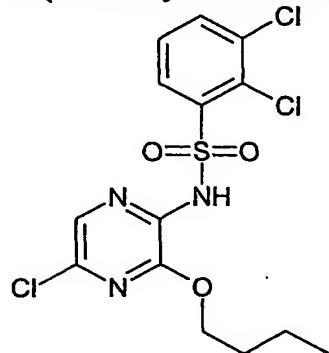
Prepared by the method of Example 31 using 2-methylsulphanylethanol (0.05g) and 2,3-dichloro-N-(3,5-dichloro-2-pyrazinyl)benzenesulphonamide (Example 74) (0.1g). Yield 0.06g.

m/e 427 ($M-1^+$, 100%)

20 1H NMR (D6-DMSO) δ 11.50-12.00 (1H, br s), 8.09 (1H, d), 7.95 (1H, d), 7.81 (1H, s), 7.60 (1H, t), 4.47 (2H, t), 2.86 (2H, t), 2.14 (3H, s)

MP 140-141°C

Example 91

***N*-(3-Butoxy-5-chloro-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide**

Prepared by the method of Example 31 using 1-butanol (0.05g) and 2,3-dichloro-*N*-(3,5-dichloro-2-pyrazinyl)benzenesulphonamide (Example 74) (0.1g). Yield 0.037g.

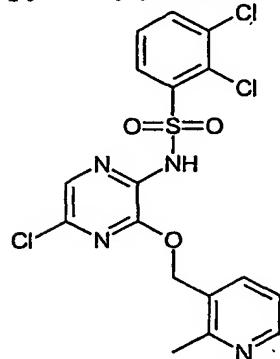
5 m/e 410 ($M+1^+$, 100%)

^1H NMR (D6-DMSO) δ 8.08 (1H, d), 7.96 (1H, d), 7.79 (1H, s), 7.57 (1H, t), 4.29 (2H, t), 1.60-1.75 (2H, m), 1.40-1.50 (2H, m), 0.95 (3H, t)

MP 133-134°C

10 **Example 92**

2,3-Dichloro-*N*-[5-chloro-3-(2-methyl-3-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide



Prepared by the method of Example 31 using (2-methyl-3-pyridinyl)methanol (0.15g) and 2,3-dichloro-*N*-(3,5-dichloro-2-pyrazinyl)benzenesulphonamide (Example 74) (0.15g).

15 Yield 0.06g

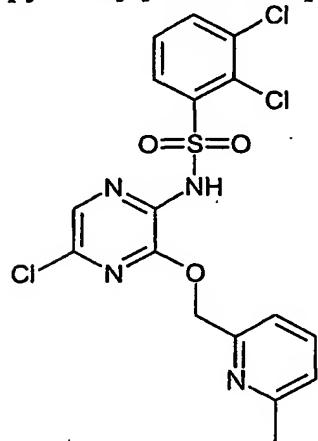
m/e 458 ($M+1^+$, 100%)

^1H NMR (D6-DMSO) δ 8.45 (1H, dd), 8.05 (1H, dd), 7.94 (1H, dd), 7.88 (1H, dd), 7.80 (1H, s), 7.53 (1H, t), 7.32 (1H, dd), 5.40 (2H, s), 2.56 (3H, s)

20 MP 214-216°C decomposes

Example 93

2,3-Dichloro-N-[5-chloro-3-(6-methyl-2-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide



Prepared by the method of Example 31 using (6-methyl-2-pyridinyl)methanol (0.15g) and

5 2,3-dichloro-N-(3,5-dichloro-2-pyrazinyl)benzenesulphonamide (Example 74) (0.15g).

Yield 0.06g.

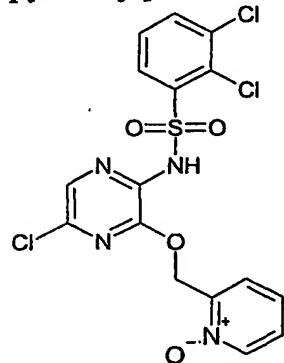
m/e 461 (M+1⁺, 100%)

¹H NMR (D6-DMSO) δ 8.08 (1H, dd), 7.91 (1H, dd), 7.84 (1H, s), 7.75 (1H, t), 7.55 (1H, t), 7.42 (1H, d), 7.24 (1H, d), 5.42 (2H, s), 2.52 (3H, s)

10 MP 158-159°C

Example 94

2,3-Dichloro-N-[5-chloro-3-(1-oxy-2-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide



15 Prepared by the method of Example 86 using 2,3-dichloro-N-[5-chloro-3-(2-

pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide (Example 89) (0.2g). Yield 0.1g.

m/e 462 (M+1⁺, 100%)

¹H NMR (D6-DMSO) δ 8.35-8.40 (1H, m), 8.09 (1H, dd), 7.80-7.90 (2H, m), 7.88 (1H, s),

20 7.58 (1H, t), 7.40-7.50 (2H, m), 5.51 (2H, s)

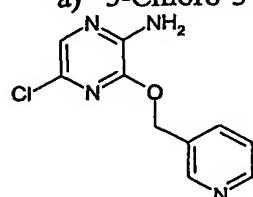
MP 222-224°C decomposes

Example 95

3-Chloro-N-[5-chloro-3-(3-pyridinylmethoxy)-2-pyrazinyl]-2-

5-methylbenzenesulphonamide

a) 5-Chloro-3-(3-pyridinylmethoxy)-2-pyrazinamine

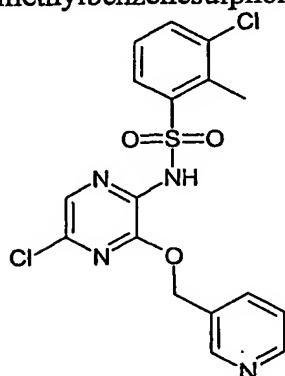


3,5-Dichloro-2-pyrazinamine (1.0g) was added to a stirred suspension of pyridine-3-

methanol (1.3g) and sodium hydride (0.70g of 60% dispersion in oil) in 1,2-dimethoxyethane (10mL). After 0.5h, 5% aqueous citric acid was added and the mixture extracted with ethyl acetate. Chromatography on silica gel eluting with ethyl acetate/*iso*-hexane mixtures gave the title compound as a white solid (0.2g). Used directly.

b) 3-Chloro-N-[5-chloro-3-(3-pyridinylmethoxy)-2-pyrazinyl]-2-

methylbenzenesulphonamide



Prepared by the method of Example 1 (reaction performed at room temperature) using 5-chloro-3-(3-pyridinylmethoxy)-2-pyrazinamine (Example 95a) (0.1g) and 3-chloro-2-

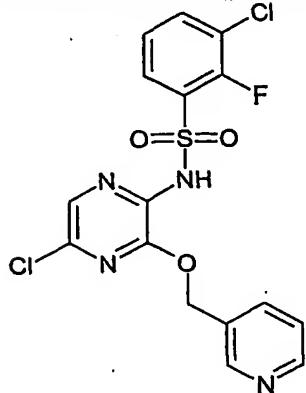
methylbenzenesulphonyl chloride (0.09g). Yield 0.012g.

m/e 425 (M+1⁺, 100%)

¹H NMR (D6-DMSO) δ 8.78 (1H, d), 8.58 (1H, dd), 7.96 (2H, dt), 7.83 (1H, s), 7.72 (1H, d), 7.46 (1H, dd), 7.40 (1H, t), 5.44 (2H, s), 2.63 (3H, s)

MP 192-193°C

3-Chloro-N-[5-chloro-3-(3-pyridinylmethoxy)-2-pyrazinyl]-2-fluorobenzenesulphonamide



Prepared by the method of Example 1 (reaction performed at room temperature) using 5-chloro-3-(3-pyridinylmethoxy)-2-pyrazinamine (Example 95a) (0.1g) and 3-chloro-2-fluorobenzenesulphonyl chloride (0.1g). Yield 0.034g.

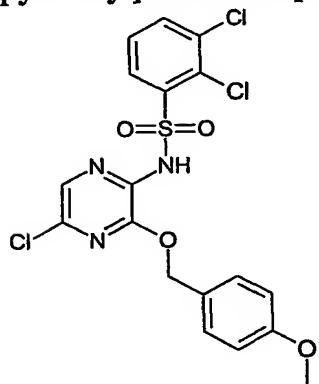
m/e 429 (M+1⁺, 100%)

¹H NMR (D₆-DMSO) δ 8.78 (1H, d), 8.60 (1H, dd), 7.99 (1H, dt), 7.80-7.90 (3H, m), 7.48 (1H, dd), 7.40 (1H, t), 5.43 (2H, s)

MP 177-178°C

Example 97

2,3-Dichloro-N-[5-chloro-3-(4-methoxyphenylmethoxy)-2-pyrazinyl]benzenesulphonamide



Prepared by the method of Example 31 using 4-methoxybenzylalcohol (0.3g) and 2,3-dichloro-N-(3,5-dichloro-2-pyrazinyl)benzenesulphonamide (Example 74) (0.5g). Yield 0.4g.

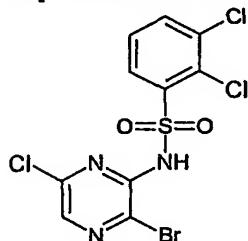
m/e 475 (M+1⁺, 100%)

¹H NMR (D6-DMSO) δ 8.05 (1H, dd), 7.91 (1H, dd), 7.81 (1H, s), 7.58 (1H, t), 7.42 (2H, d), 6.94 (2H, d), 5.32 (2H, s), 3.77 (3H, s)

MP 163-164°C

5 **Example 98**

N-[5-Bromo-6-chloro-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide



Prepared by the method of Example 1 (reaction performed at room temperature) using 3-bromo-5-chloro-2-pyrazinamine (Example 4a) (1.2g) and 2,3-dichlorobenzenesulphonyl chloride (1.4g). Yield 1.5g.

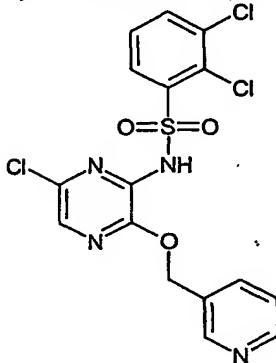
m/e 418 (M+1⁺, 100%)

¹H NMR (D6-DMSO) δ 8.07 (1H, dd), 7.90-7.80 (2H, m), 7.53 (1H, t)

MP 123-124°C

15 **Example 99**

2,3-Dichloro-N-[6-chloro-3-(3-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide



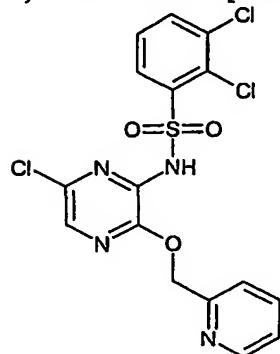
Prepared by the method of Example 31 using pyridine-3-methanol (0.22g) and N-(3-bromo-6-chloro-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide (Example 98) (0.2g).

20 Yield 0.04g.

m/e 445 (M+1⁺, 100%)

¹H NMR (D6-DMSO) δ 8.77 (1H, br s), 8.59 (1H, dd), 8.12 (1H, dd), 8.00 (1H, dt), 7.92 (1H, dd), 7.84 (1H, s), 7.58 (1H, t), 7.55-7.50 (1H, m), 5.44 (2H, s)

MP 203-204°C

Example 100**2,3-Dichloro-N-[6-chloro-3-(2-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide**

Prepared by the method of Example 31 using pyridine-2-methanol (0.22g) and *N*-(3-bromo-6-chloro-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide (Example 98) (0.2g).

Yield 0.13g.

m/e 445 (M+1⁺, 100%)

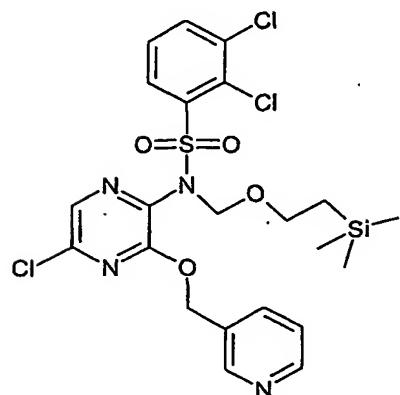
¹H NMR (D6-DMSO) δ 8.56 (1H, dd), 8.15 (1H, dd), 7.94 (1H, dd), 7.90-7.80 (2H, m), 7.65-7.60 (1H, m), 7.58 (1H, s), 7.40-7.35 (1H, m), 5.48 (2H, s)

MP 201-203°C

Example 101***N*-[5-(2-Aminoethylsulphanyl)-3-(2-pyridinylmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide**

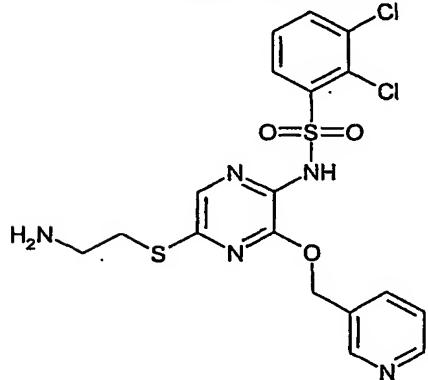
15

a) 2,3-Dichloro-*N*-[5-chloro-3-(3-pyridinylmethoxy)-2-pyrazinyl]-*N*-[2-trimethylsilylethoxymethyl]benzenesulphonamide



Prepared by the method of Example 66a using 2,3-dichloro-N-[5-chloro-3-(3-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide (Example 36) (0.5g). Yield 0.68g. Used directly.

5 b) *N*-[5-(2-Aminoethylsulphanyl)-3-(2-pyridinylmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide



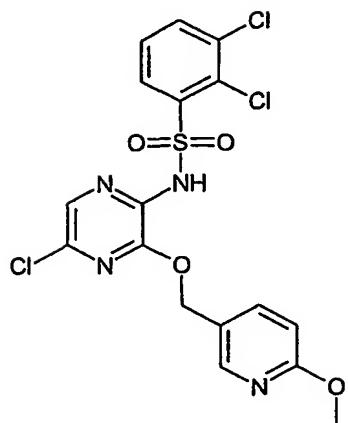
10 A mixture of 2,3-dichloro-N-[5-chloro-3-(3-pyridinylmethoxy)-2-pyrazinyl]-*N*-[2-trimethylsilyl lethoxymethyl]benzenesulphonamide (Example 101a) (0.68g), caesium carbonate (1.9g) and 2-aminoethanethiol hydrochloride (0.2g) in acetonitrile (5mL) was stirred at room temperature for 5h. Ethyl acetate was added and the mixture washed with water and brine. The organic layer was dried ($MgSO_4$) and evaporated. The residue was dissolved in trifluoracetic acid. After 1h, toluene was added and the mixture evaporated to dryness. HCl (1M in dioxane) was added and the solid collected by filtration (0.2g).

15 m/e 484 ($M-1^+$, 100%)

1H NMR (D6-DMSO) δ 8.65 (1H, s), 8.52 (1H, d), 8.20-7.60 (2H, br s), 7.96 (1H, dd), 7.82 (1H, d), 7.62 (1H, d), 7.42-7.38 (1H, m), 7.35 (1H, t), 7.30 (1H, s), 5.24 (2H, s), 3.05-3.00 (2H, m), 2.85-2.80 (2H, m)

20 **Example 102**

2,3-Dichloro-*N*-[5-chloro-3-(6-methoxy-3-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide



Prepared by the method of Example 31 using (6-methoxy-3-pyridinyl)methanol (0.3g) and 2,3-dichloro-N-(3,5-dichloro-2-pyrazinyl)benzenesulphonamide (Example 74) (0.3g).

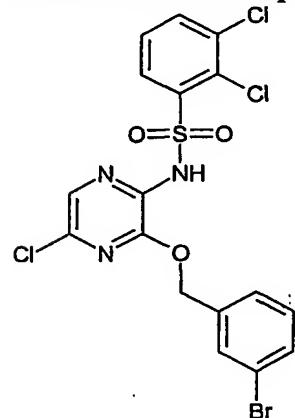
Yield 0.15g.

5 m/e 474 (M-1⁺, 100%)

¹H NMR (D6-DMSO) δ 8.32 (1H, d), 8.04 (1H, dd), 7.91 (1H, dd), 7.85-7.80 (2H, m), 7.86 (1H, d), 7.55 (1H, t), 6.86 (1H, dd), 5.33 (2H, s), 3.87 (3H, s)

Example 103

10 *N*-[3-(3-Bromophenylmethoxy)-5-chloro-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide.

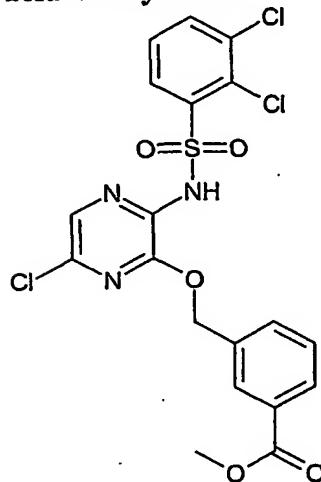


Prepared by the method of Example 31b using 3-bromobenzylalcohol (1.3g) and 2,3-dichloro-N-(3,5-dichloro-2-pyrazinyl)benzenesulphonamide (Example 74) (1.1g). Yield

15 1.1g.

m/e 522 (M+1⁺, 100%)

¹H NMR (D6-DMSO) δ 8.07 (1H, dd), 7.92 (1H, dd), 7.85 (1H, s), 7.78 (1H, s), 7.60-7.50 (3H, m), 7.37 (1H, t), 5.40 (2H, s)

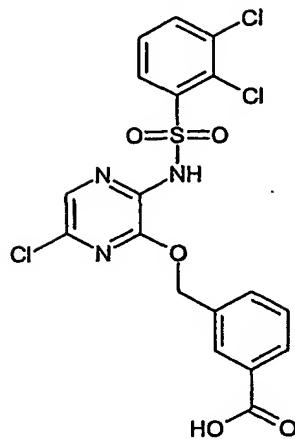
Example 104**3-[6-Chloro-3-(2,3-dichlorobenzenesulphonylamino)-2-pyrazinyloxymethyl]benzoic acid methyl ester**

5 *N*-[3-(3-Bromophenylmethoxy)-5-chloro-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide (Example 103) (1.0g) and *bis*(triphenylphosphine)palladium dichloride (0.4g) in methanol (15mL) and triethylamine (7mL) was heated at 100°C under an atmosphere of carbon monoxide (6 barr). After 20h, the mixture was filtered and evaporated. The residue was dissolved in ethyl acetate. The organic solution was washed with brine, aqueous citric acid, dried (MgSO_4) and evaporated. Chromatography on silica gel eluting with ethyl acetate/*iso*-hexane mixtures gave the title compound as a white solid (0.65g).

10 $^1\text{H NMR}$ (D6-DMSO) δ 8.11 (1H, s), 8.05 (1H, dd), 7.95 (1H, d), 7.90 (1H, dd), 7.84 (1H, s), 7.80 (1H, d), 7.60-7.50 (2H, m), 5.46 (2H, s), 3.88 (3H, s)

15 MP 175-176°C

Example 105**3-[6-Chloro-3-(2,3-dichlorobenzenesulphonylamino)-2-pyrazinyloxymethyl]benzoic acid**



A mixture of 3-[6-chloro-3-(2,3-dichlorobenzenesulphonylamino)-2-pyrazinyl]benzoic acid methyl ester (Example 104) (0.3g) and lithium hydroxide hydrate (0.2g) in water (5mL) and methanol (5mL) was stirred at room temperature. After 5 3h, hydrochloric acid (2M) was added to acidify the mixture and the solid product was collected by filtration and dried (0.25g).

m/e 489 (M+1⁺, 100%)

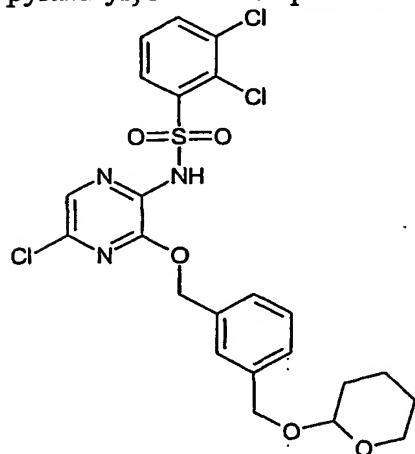
¹H NMR (D6-DMSO) δ 13.10-13.00 (1H, br s), 12.00-11.80 (1H, br s), 8.10 (1H, s), 8.05 (1H, dd), 7.85-7.95 (2H, m), 7.82 (1H, s), 7.76 (1H, d), 7.54 (2H, t), 5.46 (2H, s)

10 MP 218-224°C decomposes

Example 106

2,3-Dichloro-N-[5-chloro-3-(3-hydroxymethylphenylmethoxy)-2-pyrazinyl]benzenesulphonamide

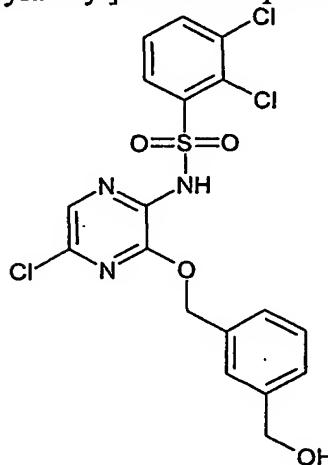
15 a) 2,3-Dichloro-N-[5-chloro-3-[3-(tetrahydro-2-pyranyloxymethyl)phenylmethoxy]-2-pyrazinyl]benzenesulphonamide



Prepared by the method of Example 31 using [3-(tetrahydro-2-pyranoyloxymethyl)phenyl]methanol (1.99g) and 2,3-dichloro-N-(3,5-dichloro-2-pyrazinyl)benzenesulphonamide (Example 74) (1.0g). Yield 1.0g. Used directly.

5

b) 2,3-Dichloro-N-[5-chloro-3-(3-hydroxymethylphenylmethoxy)-2-pyrazinyl]benzenesulphonamide



2,3-Dichloro-N-[5-chloro-3-[3-(tetrahydro-2-pyranoyloxymethyl)phenylmethoxy]-2-pyrazinyl]benzenesulphonamide (Example 106a) (1.0g) in acetic acid (40mL), water (10mL) and tetrahydrofuran (20mL) was heated at 45°C for 16h and the solution was evaporated to dryness. Chromatography on silica gel eluting with ethyl acetate/iso-hexane mixtures gave the title compound as a white solid (0.6g).

m/e 475 (M+1⁺, 100%)

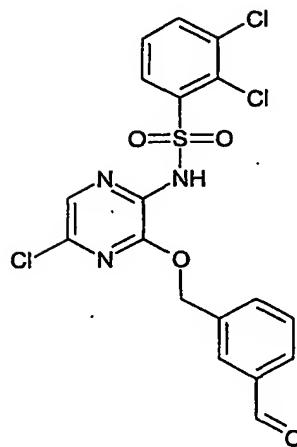
¹H NMR (D6-DMSO) δ 8.05 (1H, dd), 7.91 (1H, dd), 7.82 (1H, s), 7.55 (1H, t), 7.43 (1H, s), 7.40-7.25 (3H, m), 5.39 (2H, s), 4.52 (2H, s)

MP 162-163°C

Example 107

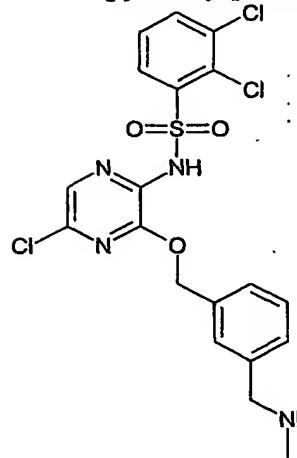
2,3-Dichloro-N-[5-chloro-3-(3-methylaminomethylphenylmethoxy)-2-pyrazinyl]benzenesulphonamide

a) 2,3-Dichloro-N-[5-chloro-3-(3-formylphenylmethoxy)-2-pyrazinyl]benzenesulphonamide



2,3-Dichloro-N-[5-chloro-3-(3-hydroxymethylphenylmethoxy)-2-pyrazinyl]benzenesulphonamide (Example 106) (0.6g) and manganese dioxide (1.0g) in tetrahydrofuran (5mL) was stirred at room temperature for 16h. The mixture was diluted with dichloromethane and filtered through celite. The solution was evaporated to dryness and the product crystallised from diethyl ether (0.4g). Used directly.

5 b) 2,3-Dichloro-N-[5-chloro-3-(3-methylaminomethylphenylmethoxy)-2-pyrazinyl]benzenesulphonamide



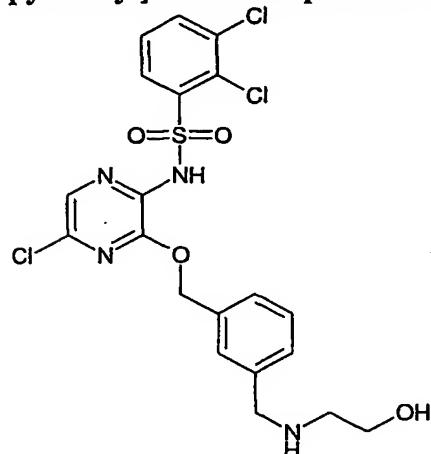
10 A mixture of 2,3-dichloro-N-[5-chloro-3-(3-formylphenylmethoxy)-2-pyrazinyl]benzenesulphonamide (Example 107a) (0.1g), methylamine (2mL of a 2M solution in tetrahydrofuran) and acetic acid (0.2mL) in methanol (2mL) was stirred at room temperature. After 2h, sodium cyanoborohydride (0.03g) was added. After 0.5h, water (2mL) was added and the mixture evaporated to dryness. Chromatography on silica gel eluting with methanol/dichloromethane mixtures gave the title compound as a white solid (0.035g).

15 m/e 487 ($M+1^+$, 100%)

¹H NMR (D6-DMSO) δ 8.90-8.60 (2H, br s), 8.02 (1H, d), 7.90-7.80 (1H, m), 7.80-7.60 (1H, m), 7.59 (1H, d), 7.55-7.40 (4H, m), 5.40 (2H, s), 4.08 (2H, s), 2.59 (3H, s)
 MP 167-168°C

5 **Example 108**

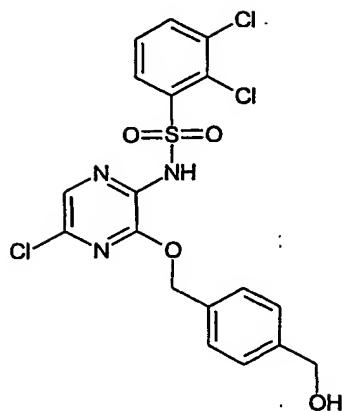
2,3-Dichloro-N-[5-chloro-3-{3-[(2-hydroxyethylamino)methyl]phenylmethoxy}-2-pyrazinyl]benzenesulphonamide



Prepared by the method of Example 107b using 2,3-dichloro-N-[5-chloro-3-(3-formylphenylmethoxy)-2-pyrazinyl]benzenesulphonamide (Example 107a) (0.1g) and 2-aminoethanol (0.05g). Yield 0.035g.
 m/e 517 (M+1⁺, 100%)
¹H NMR (D6-DMSO) δ 9.00-8.80 (2H, br s), 7.93 (1H, d), 7.80-7.20 (7H, m), 5.28 (2H, s), 5.21 (1H, t), 4.20 (2H, s), 3.80-3.60 (2H, m), 3.05-2.95 (2H, m)
 15 MP 196-198°C

Example 109

2,3-Dichloro-N-[5-chloro-3-(4-hydroxymethylphenylmethoxy)-2-pyrazinyl]benzenesulphonamide



Prepared by the method of Examples 106a and 106b using [4-(tetrahydro-2-pyranyloxymethyl)phenyl]methanol (2.0g) and 2,3-dichloro-N-(3,5-dichloro-2-pyrazinyl)benzenesulphonamide (Example 74) (1.0g). Yield 0.7g.

5 m/e 474 (M-1⁺, 100%)

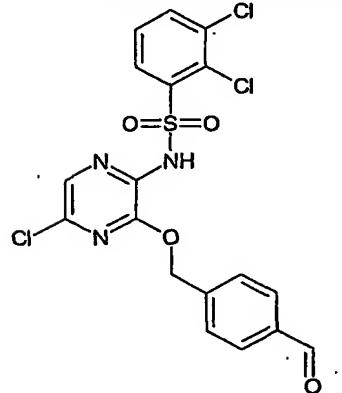
¹H NMR (D6-DMSO) δ 8.05 (1H, dd), 7.91 (1H, dd), 7.83 (1H, s), 7.55 (1H, t), 7.46 (2H, d), 7.33 (2H, d), 5.38 (2H, s), 4.51 (2H, s)

MP 177-178°C

10 **Example 110**

2,3-Dichloro-N-[5-chloro-3-{4-[(2-hydroxyethylamino)methyl]phenylmethoxy}-2-pyrazinyl]benzenesulphonamide

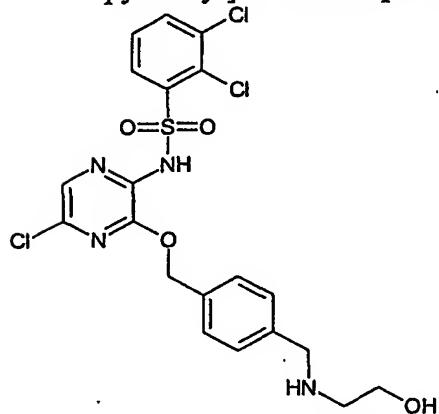
a) 2,3-Dichloro-N-[5-chloro-3-(4-formylphenylmethoxy)-2-pyrazinyl]benzenesulphonamide



15

Prepared by the method of Example 107a using 2,3-dichloro-N-[5-chloro-3-(4-hydroxymethylphenylmethoxy)-2-pyrazinyl]benzenesulphonamide (Example 109) (0.65g). Yield 0.64g. Used directly.

b) 2,3-Dichloro-N-(5-chloro-3-{4-[(2-hydroxyethylamino)methyl]phenylmethoxy}-2-pyrazinyl]benzenesulphonamide



Prepared by the method of Example 107b using 2,3-dichloro-N-[5-chloro-4-(3-

5 formylphenylmethoxy)-2-pyrazinyl]benzenesulphonamide (Example 110a) (0.1g) and 2-aminoethanol (0.05g). Yield 0.028g.

m/e 517 (M+1⁺, 100%)

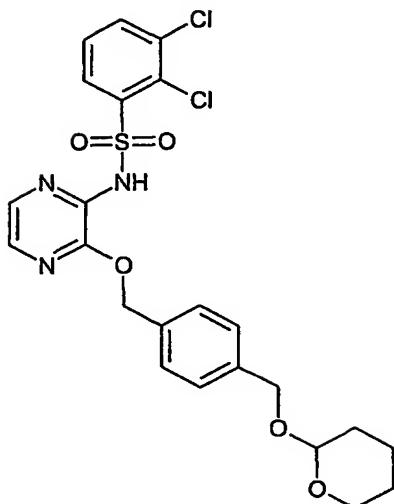
10 ¹H NMR (D6-DMSO) δ 8.75 (2H, br s), 7.93 (1H, dd), 7.61 (1H, dd), 7.54 (4H, s), 7.35 (1H, t), 7.26 (1H, s), 5.26 (2H, s), 5.18 (1H, t), 4.18 (2H, s), 3.70-3.60 (2H, m), 3.00-2.95 (2H, m)

MP 202-205°C

Example 111

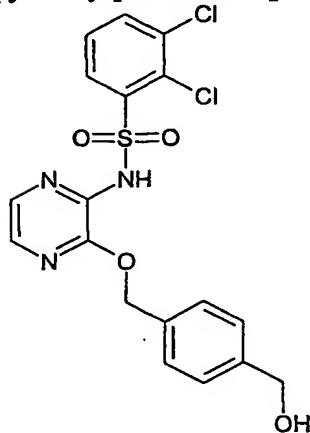
15 2,3-Dichloro-N-[3-(4-hydroxymethylphenylmethoxy)-2-pyrazinyl]benzenesulphonamide

a) 2,3-Dichloro-N-{3-[4-(tetrahydro-2-pyranyloxymethyl)phenylmethoxy]-2-pyrazinyl}benzenesulphonamide



2,3-Dichloro-N-(3-chloro-2-pyrazinyl)benzenesulphonamide (Example 28a) (0.1g), [4-(tetrahydro-2-pyranyloxymethyl)phenyl]methanol (0.27g) and potassium *tert*-butoxide (2mL of a 1M solution in tetrahydrofuran) in *N*-methylpyrrolidinone (1mL) was stirred at 5 50°C. After 2h, aqueous citric acid was added and the mixture extracted with ethyl acetate. The organic solution was washed with water and brine and evaporated to dryness. Used directly.

10 b) 2,3-Dichloro-N-[3-(4-hydroxymethylphenylmethoxy)-2-pyrazinyl]benzenesulphonamide



15 2,3-Dichloro-N-[3-[4-(tetrahydro-2-pyranyloxymethyl)phenylmethoxy]-2-pyrazinyl]benzenesulphonamide (Example 111a) in acetic acid (10mL), water (2.5mL) and tetrahydrofuran (5mL) was heated at 45°C for 16h and the solution was evaporated to dryness. Chromatography on silica gel eluting with ethyl acetate/iso-hexane mixtures gave the title compound as a white solid (0.022g).
m/e 440 (M+1⁺, 100%)

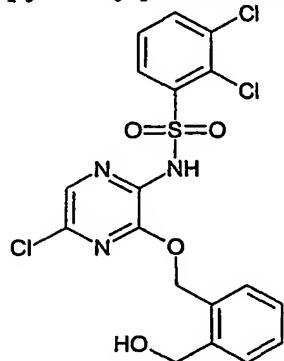
¹H NMR (D6-DMSO) δ 8.08 (1H, dd), 7.91 (1H, dd), 7.90-7.70 (1H, br s), 7.70-7.60 (1H, br s), 7.55 (1H, t), 7.42 (2H, d), 7.31 (2H, d), 5.39 (2H, s), 5.20-5.05 (1H, br s), 4.49 (2H, s)

MP 160-161°C

5

Example 112

2,3-Dichloro-N-[5-chloro-3-(2-hydroxymethylphenylmethoxy)-2-pyrazinyl]benzenesulphonamide



10 2,3-Dichloro-N-(3,5-dichloro-2-pyrazinyl)benzenesulphonamide (Example 74). (0.15g), (2-hydroxymethylphenyl)methanol (0.27g) and potassium *tert*-butoxide (3mL of a 1M solution in tetrahydrofuran) in *N*-methylpyrrolidinone (2mL) was stirred at room temperature. After 1h, aqueous citric acid was added and the mixture extracted with ethyl acetate. The organic solution was washed with water and brine and evaporated to dryness.

15 Chromatography on silica gel eluting with ethyl acetate/*iso*-hexane mixtures gave the title compound as a white solid (0.027g).

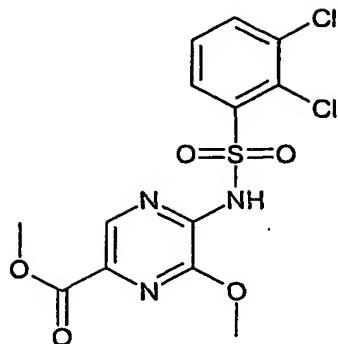
m/e 474 (M+1⁺, 100%)

¹H NMR (D6-DMSO) δ 8.06 (1H, dd), 7.90 (1H, dd), 7.81 (1H, s), 7.60-7.40 (3H, m), 7.37 (1H, t), 7.29 (1H, t), 5.45 (2H, s), 4.64 (2H, s)

20 MP 145-146°C

Example 113

5-(2,3-Dichlorobenzenesulphonylamino)-6-methoxypyrazine-2-carboxylic acid, methyl ester



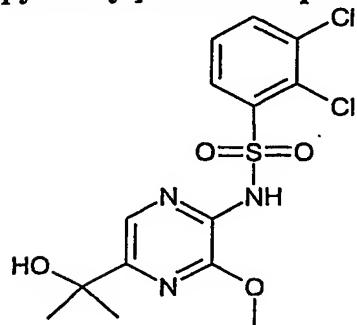
N-(5-Bromo-3-methoxy-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide (Example 8) (6.5g) and dichloro[1,1'-*bis*(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct (0.7g) in methanol (30mL) and triethylamine (10mL) was heated at 100°C under an atmosphere of carbon monoxide (6 bar). After 5h, the mixture was filtered and evaporated. The residue was dissolved in ethyl acetate. The organic solution was washed with brine, aqueous citric acid, dried (MgSO_4) and evaporated. Chromatography on silica gel eluting with ethyl acetate/*iso*-hexane mixtures gave the title compound as a white solid (4.8g).
 m/e 392 ($\text{M}+1^+$, 100%)

10 ^1H NMR ($\text{D}_6\text{-DMSO}$) δ 8.13 (2H, dd), 7.95 (1H, dd), 7.60 (1H, t), 3.95 (3H, s), 3.82 (3H, s)

MP 120-121°C

Example 114

15 2,3-Dichloro-*N*-(5-(1-hydroxy-1-methylethyl)-3-methoxy-2-pyrazinyl]benzenesulphonamide



Methylmagnesium bromide (3mL of a 3M solution in diethyl ether) was added over 3 minutes to a stirred solution of 5-(2,3-dichlorobenzenesulfonylamino)-6-methoxypyrazine-2-carboxylic acid, methyl ester (Example 113) (0.3g) in tetrahydrofuran (10mL) cooled in an ice/water bath. After a further 5 minutes, aqueous citric acid was added and the mixture extracted with ethyl acetate. The organic solution was evaporated to

dryness. Chromatography on silica gel eluting with methanol/dichloromethane mixtures gave the title compound as a white solid (0.15g).

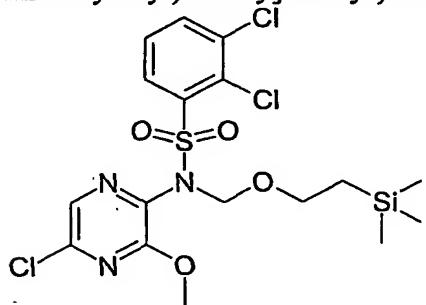
m/e 392 (M+1⁺, 100%)

¹H NMR (D6-DMSO) δ 11.40-11.30 (1H, br s), 8.07 (1H, dd), 7.93 (1H, d), 7.90-7.80 (1H, br s), 7.59 (1H, t), 5.10-5.05 (1H, br s), 3.88 (3H, s), 1.39 (6H, s)

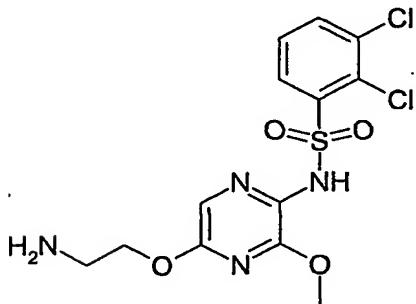
MP 192-193°C

Example 115

10 *N*-[5-(2-Aminoethoxy)-3-methoxy-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide
a) 2,3-Dichloro-*N*-(5-chloro-3-methoxy-2-pyrazinyl)-*N*-{[2-(trimethylsilyl)ethoxy]methyl}benzenesulphonamide



15 Prepared by the method of Example 66a using 2,3-dichloro-*N*-(5-chloro-3-methoxy-2-pyrazinyl)benzenesulphonamide (Example 5) (7.0g). Yield 9.8g. Used directly.



b) *N*-[5-(2-aminoethoxy)-3-methoxy-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide

2,3-Dichloro-*N*-(5-chloro-3-methoxy-2-pyrazinyl)-*N*-{[2-(trimethylsilyl)ethoxy]methyl}benzenesulphonamide (Example 115a) (0.25g) was added to 20 a mixture of ethanamine (0.05mL) and sodium hydride (0.035g of a 60% dispersion in oil) in 1,2-dimethoxyethane (15mL) at room temperature. After 2h, the mixture was partitioned between water and ethyl acetate. The organic layer was washed with brine, dried (MgSO₄) and evaporated to dryness. Chromatography on silica gel eluting with

methanol/dichloromethane mixtures gave the title compound containing the SEM ([2-(trimethylsilyl)ethoxy]methyl) protecting group as an oil (0.14g). Trifluoroacetic acid (1mL) and dichloromethane (3mL) were added. After 0.5h at room temperature, toluene was added and the solution evaporated to dryness. HCl (4M in dioxane) was added and the mixture evaporated to dryness. The product was crystallised from diethyl ether (0.075g).

m/e 393 (M+1⁺, 100%)

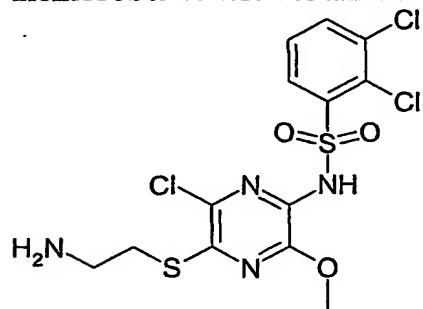
¹H NMR (D6-DMSO) δ 10.90 (1H, br s), 8.07 (2H, br s), 7.99-7.92 (2H, m), 7.56 (1H, t), 7.49 (1H, s), 4.45 (2H, t), 3.84 (3H, s), 3.25-3.20 (2H, m)

MP 200-205°C

10

Example 116

N-{5-[(2-Aminoethyl)thio]-6-chloro-3-methoxy-2-pyrazinyl}-2,3-dichlorobenzenesulfonamide



15 Prepared by the method of Example 101b using 2,3-dichloro-N-(5,6-dichloro-3-methoxy-2-pyrazinyl)-N-{[2-(trimethylsilyl)ethoxy]methyl}benzenesulphonamide (Example 66a) (0.27g). Yield 0.055g.

m/e 443 (M+1⁺, 100%)

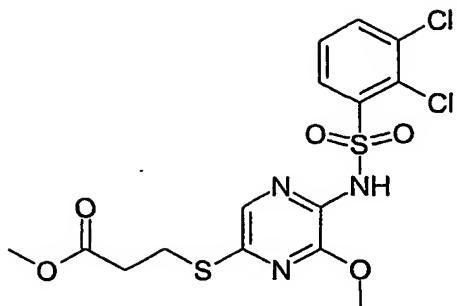
¹H NMR (D6-DMSO) δ 8.09 (1H, d), 7.90 (1H, d), 7.58 (1H, t), 3.95 (3H, s), 3.33 (2H, t), 20 3.14 (2H, t).

MP 185-190°C

Example 117

3-[(5-{{(2,3-Dichlorophenyl)sulphonyl}amino}-6-methoxy-2-pyrazinyl)thio]propanoic acid, methyl ester

25



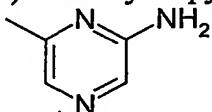
Prepared by the method of Example 101b using
 2,3-dichloro-N-(5-chloro-3-methoxy-2-pyrazinyl)-N-[(2-(trimethylsilyl)ethoxy)methyl]benzenesulphonamide (Example 115a) (0.25g) and 3-
 5 mercaptopropionic acid, methyl ester (0.06mL). Yield 0.1g.
 m/e 452 (M+1⁺, 100%)
¹H NMR (D6-DMSO) δ 11.35 (1H, br s), 8.03 (1H, d), 7.93 (1H, d), 7.66 (1H, s), 7.57
 (1H, t), 3.90 (3H, s), 3.58 (3H, s), 3.29 (2H, t), 2.72 (2H, t).
 MP 146-148°C

10

Example 118

2,3-Dichloro-N-[5-bromo-3-methoxy-6-methyl-2-pyrazinyl]benzenesulphonamide

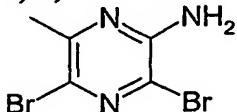
a) 6-Methyl-2-pyrazinamine



15 Dimethylzinc (100mL of a 2M solution in toluene) was added dropwise over 0.5h to a stirred solution of 6-chloro-2-pyrazinamine (12.9g) and [1,3-
 bis(diphenylphosphino)propane]nickel(II) chloride (5.4g) in dioxane (200mL) under a nitrogen atmosphere. The reaction mixture was heated at reflux for 18h, then cooled to room temperature and quenched cautiously with *iso*-propanol (30mL) and methanol (50mL). After removal of solvent *in vacuo*, the residue was partitioned between dichloromethane and aqueous ammonium chloride. The organic phase was filtered through celite, dried (MgSO₄), filtered and evaporated to give the crude product as an orange solid. Chromatography on silica gel eluting with ethyl acetate/methanol mixtures gave the title compound (5.1g). Used directly.

20

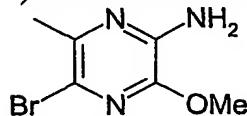
b) 3,5-Dibromo-6-methyl-2-pyrazinamine



A solution of bromine (1.85g) in chloroform (5mL) was added dropwise to a stirred solution of 2-amino-6-methylpyrazine (Example 118a) (0.6g) in chloroform (50mL). The reaction mixture was stirred at room temperature for 0.5h, then washed twice with water, dried (MgSO_4), filtered and evaporated to give the crude product as an orange solid.

5 Chromatography on silica gel eluting with dichloromethane gave the title compound (0.95g). Used directly.

c) 5-Bromo-3-methoxy-6-methyl-2-pyrazinamine

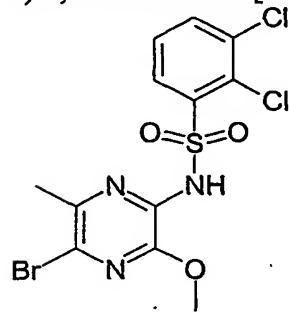


10 A solution of 3,5-dibromo-6-methyl-2-pyrazinamine (Example 118b) (0.9g) was added to a solution of sodium (0.39g) in methanol (30mL) was heated at reflux for 18h. After removal of solvent *in vacuo*, the residue was partitioned between water and dichloromethane, and the organic phase dried (MgSO_4), filtered and evaporated to give the title compound as a pale yellow solid (0.58g).

15 m/e 218/220 ($\text{M}+1^+$, 100%)

$^1\text{H NMR}$ (CDCl_3) δ 4.70 (2H, br s), 3.97 (3H, s), 2.40 (3H, s)

d) 2,3-Dichloro-*N*-(5-bromo-3-methoxy-6-methyl-2-pyrazinyl)benzenesulphonamide



20 Sodium hydride (0.5g of a 60% dispersion in oil) was added to a solution of 5-bromo-3-methoxy-6-methyl-2-pyrazinamine (Example 118c) (0.55g) in *N*-methylpyrrolidinone (25mL). The resultant dark solution was stirred at room temperature for 0.5h before a solution of 2,3-dichlorobenzenesulphonyl chloride (0.67g) in *N*-methylpyrrolidinone (5mL) was added dropwise. The reaction mixture was stirred at room temperature for 3h, then quenched with aqueous ammonium chloride and partitioned between ethyl acetate and aqueous ammonium chloride (x5). the organic phase was dried (MgSO_4), filtered and evaporated to give the crude product. Chromatography on silica gel eluting with dichloromethane/ acetic acid (200:1) gave the title compound as a pale yellow solid (0.38g).

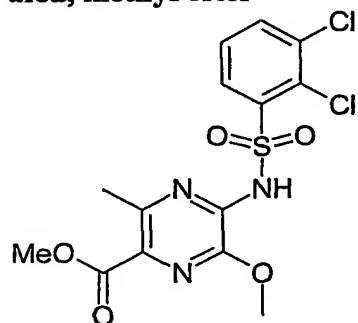
m/e 424/426/428 (M-1⁺, 100%)

¹H NMR (CDCl₃) δ 8.29 (1H, d), 7.69 (2H, d), 7.41 (1H, t), 4.01 (3H, s), 2.27 (3H, s)

MP 146-148°C

5 **Example 119**

5-(2,3-Dichlorobenzenesulphonylamino)-6-methoxy-3-methylpyrazine-2-carboxylic acid, methyl ester



Prepared by the method of Example 113 using 2,3-dichloro-N-[5-bromo-3-methoxy-6-

10 methylpyrazinyl)benzenesulphonamide (Example 118) (0.35g). Yield 0.27g.

m/e 404/406 (M-1⁺, 100%)

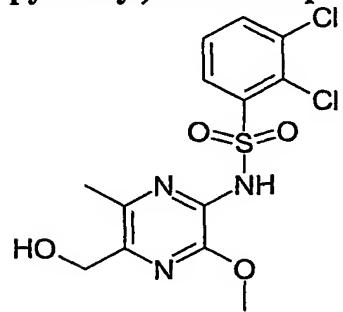
¹H NMR (CDCl₃) δ 8.32 (1H, br s), 8.10 (1H, br s), 7.70 (1H, d), 7.42 (1H, t) 4.06 (3H, s), 3.90 (3H, s), 2.50 (3H, br s).

MP 149-150°C

15

Example 120

2,3-Dichloro-N-[5-(hydroxymethyl)-3-methoxy-6-methyl-2-pyrazinyl]benzenesulphonamide



20 To a stirred solution of 5-(2,3-dichlorobenzenesulphonylamino)-6-methoxy-3-methylpyrazine-2-carboxylic acid, methyl ester (Example 119) (0.19g) in tetrahydrofuran (10mL) under an atmosphere of nitrogen was added a solution of lithium triethylborohydride (1.7mL of a 1M solution in tetrahydrofuran). The reaction mixture was stirred at room temperature for 1h, before quenching with aqueous ammonium chloride

and extraction into dichloromethane. The organic phase was dried ($MgSO_4$), filtered and evaporated to give the crude product as a colourless oil. Chromatography on silica gel eluting with dichloromethane/ethyl acetate/acetic acid (150:50:1) gave the title compound as a white solid (0.38g).

5 m/e 378 ($M+1^+$, 100%)

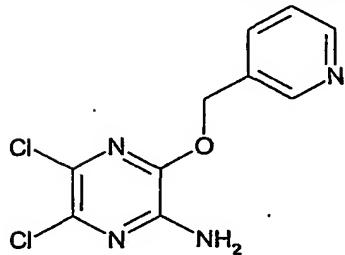
1H NMR ($CDCl_3$) δ 8.31 (1H, br d), 7.77 (1H, br s), 7.68 (1H, d), 7.41 (1H, t), 4.55 (2H, d), 4.03 (3H, s), 3.12 (1H, br s), 2.13 (3H, br s).

MP 175-177°C

10 **Example 121**

2,3-Dichloro-N-[5,6-dichloro-3-(3-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide

a) 5,6-Dichloro-3-(3-pyridinylmethoxy)-2-pyrazinamine

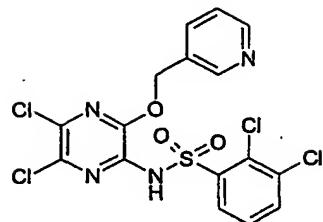


15 To a stirred suspension of sodium hydride (1.20g of a 60% dispersion in oil) in dry dimethoxymethane (40 mL) was added pyridine-3-methanol (2.18g) in 1,2-dimethoxymethane (10 mL). The resulting suspension was stirred at room temperature for 0.5h and then 3,5,6-trichloro-2-aminopyrazine (1.2g) was added and the mixture stirred at 20 70°C for 4h. The reaction mixture was cooled and cautiously added to water (100 mL) and neutralised with 2M hydrochloric acid. The mixture was extracted with ethyl acetate (2x50 mL), dried ($MgSO_4$), filtered and concentrated. The residue was purified by chromatography on silical gel eluting with ethyl acetate to afford the sub-titled compound as a white solid (0.29 g).

25 1H NMR ($CDCl_3$) δ 8.73 (1H, s), 8.63 (1H, d), 7.8 (1H, d), 7.35 (1H, dd), 5.42 (2H, s), 4.92 (2H, br s).

b) 2,3-Dichloro-N-[5,6-dichloro-3-(3-pyridinylmethoxy)-2-

30 pyrazinyl]benzenesulphonamide



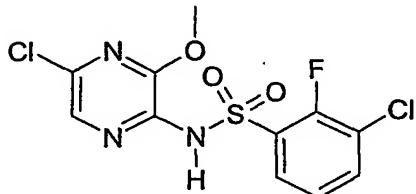
Prepared by the method of Example 1 (reaction performed at room temperature) using 5,6-dichloro-3-(3-pyridinylmethoxy)-2-pyrazinamine (Example 121a) (0.27g) and 2,3-dichlorobenzenesulphonyl chloride (0.27g). Yield 0.17g.

5 m/e 479 ($M+1^+$, 100%)

¹H NMR (D6-DMSO) δ 8.8 (1H, s), 8.63 (1H, d), 8.11 (1H, d), 8.06 (1H, d), 7.58-7.52 (2H, m), 5.41 (2H, s).

Example 122

10 3-Chloro-N-(5-chloro-3-methoxy-2-pyrazinyl)-2-fluorobenzenesulphonamide



Prepared by the method of Example 1 (reaction performed at room temperature) using 5-chloro-3-methoxy-2-pyrazinamine (0.16g) and 3-chloro-2-fluorobenzenesulphonyl chloride (0.27g). Yield 0.22g.

15 m/e 354, 352 ($M+1^+$, 100%)

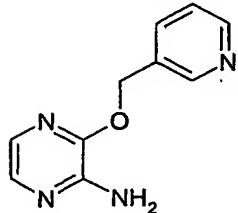
¹H NMR (D6-DMSO) δ 7.94-7.86 (2H, m), 7.82 (1H, s), 7.43 (1H, dt), 3.92 (3H, s).

MP 156-157°C

Example 123

20 3-Chloro-2-fluoro-N-[3-(3-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide

a) 3-(3-Pyridinylmethoxy)-2-pyrazinamine

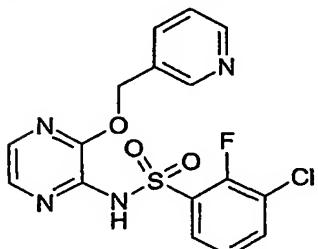


Prepared as for Example 121a using 3-chloro-2-aminopyrazine (0.5 g), pyridine-3-methanol (0.42g) and sodium hydride (0.31g of a 60% dispersion in oil) in *N*-methylpyrrolidinone (5 mL) to afford the sub-titled compound as a solid (0.62 g).

¹H NMR (CDCl₃) δ 8.73 (1H, d), 8.60 (1H, d), 7.78 (1H, d), 7.60 (1H, d), 7.42 (1H, d), 7.32 (1H, dd), 5.43 (2H, s), 4.77 (2H, br).

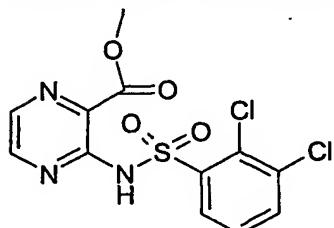
MP 120-122°C

b) 3-Chloro-2-fluoro-*N*-[3-(3-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide



To a stirred solution of 3-(3-pyridinylmethoxy)-2-pyrazinamine (Example 122a) (0.404 g) in dichloromethane (5mL) and pyridine (1 mL) was added *iso*-butylchloroformate (0.3mL) and the resulting solution stirred for 20 hours. The reaction mixture was poured into water (20mL) and extracted into ethyl acetate (2x20mL). The combined extracts were dried (MgSO₄), filtered and concentrated to afford an oil (0.51 g) that was used without further purification. A portion of the residue (0.15g) was dissolved in 1,2-dimethoxymethane (2 mL) and sodium hydride (0.030g of 60% dispersion in oil) added. The resulting suspension was stirred for 15 minutes and then 3-chloro-2-fluorobenzenesulfonyl chloride (0.137g) in dimethoxymethane (1 mL) was added. The resulting solution was stirred at room temperature for 6h. The reaction mixture was poured into water (20mL) and extracted into ethyl acetate (2x20mL). The combined extracts were dried (MgSO₄), filtered and concentrated to afford an oil that was dissolved into methanol (5mL) and water (2mL) and sodium hydroxide (0.04g) was added. The mixture was heated to 60°C for 1 hour, cooled and was poured into water (20mL) and extracted into ethyl acetate (2x20mL). The combined extracts were dried (MgSO₄), filtered and concentrated to afford an oil that was purified by chromatography on silica gel eluting with ethyl acetate/*iso*-hexane mixtures followed by ethyl acetate to afford the title compound (0.067g) as a white solid. m/e 395, 397 (M+1⁺, 100%)

¹H NMR (CDCl₃) δ 8.69 (1H, s), 8.62 (1H, d), 8.06 (1H, t), 7.78 (1H, d), 7.68 (1H, d), 7.69-7.60 (2H, m), 7.34 (1H, dd), 7.26 (1H, dd), 5.43 (2H, s).

Example 124**3-{[(2,3-Dichlorophenyl)sulphonyl]amino}pyrazine-2-carboxylic acid, methyl ester**

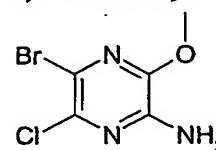
To a stirred solution of 2,3-dichlorobenzenesulphonyl chloride (0.246g) and methyl-3-aminopyrazine-2-carboxylate (0.153g) in 1,2-dimethoxymethane (3mL) was added portionwise sodium hydride (0.1g of a 60% dispersion in oil) over 1 hour. The mixture was stirred at room temperature for 20h, was poured into water (20mL) and extracted into ethyl acetate (2x20mL). The combined extracts were dried (MgSO_4), filtered and concentrated to afford an oil that was purified by chromatography on silica gel eluting with dichloromethane to afford the titled compound (0.085g) as a white solid.

m/e 362/364 ($\text{M}+1^+$, 100%)

$^1\text{H NMR}$ (CDCl_3) δ 10.97 (1H, s), 8.32 (1H, dd), 8.31 (1H, d), 8.25 (1H, d), 7.68 (1H, dd), 7.42 (1H, t), 4.08 (3H, s).

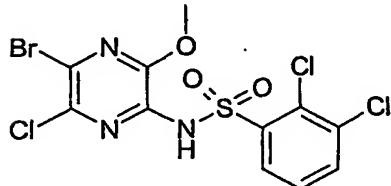
MP 177-178°C

15

Example 125***N*-(5-Bromo-6-chloro-3-methoxy-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide****a) 3-Methoxy-5-bromo-6-chloro-2-pyrazinamine**

A stirred solution of 2-amino-6-chloropyrazine (2.0g) and *N*-bromosuccinimide (13.71g) in chloroform (100 mL) was heated to reflux for 20 hours. The reaction mixture was cooled and concentrated onto silica gel (20g) and the residue loaded onto a column of silica gel (5cm x 2cm) and the column was eluted with dichloromethane. Concentration afforded 3,5-dibromo-6-chloro-2-aminopyrazine that was dissolved into methanol (200 mL) and sodium methoxide (32g of a 25% solution in methanol) added. The reaction was heated to 70°C for 1.5h, cooled and concentrated to approx. 50 mL capacity. The reaction mixture was poured into water (200mL) and the sub-titled adduct (2.0g) collected as an off-white solid.

m/e 235, 237 ($\text{M}+1^+$, 100%)

b) *N*-(5-Bromo-6-chloro-3-methoxy-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide

Procedure as for Example 1 (reaction performed at room temperature) using 3-methoxy-5-bromo-6-chloro-2-pyrazinamine (Example 125a) (0.5g) and 2,3-dichlorobenzenesulphonyl chloride (2.21g). Yield 3.2g.

m/e 445, 447 (M-1⁺, 100%)

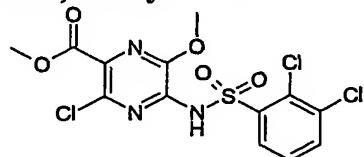
¹H NMR (CDCl₃) δ 8.32 (1H, dd), 7.79 (1H, br), 7.72 (1H, dd), 7.45 (1H, t), 4.05 (3H, s).

MP 177-178°C

10

Example 126

3-Chloro-5-{[(2,3-dichlorophenyl)sulphonyl]amino}-6-methoxypyrazine-2-carboxylic acid, methyl ester



15 Prepared by the method of Example 113 using *N*-(5-bromo-6-chloro-3-methoxypyrazin-2-yl)-2,3-dichlorobenzenesulfonamide (Example 125) (1.0g). Yield 0.92g.

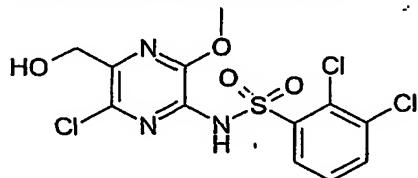
m/e 426, 428 (M-1⁺, 100%)

¹H NMR (CDCl₃) δ 8.36 (1H, dd), 8.05 (1H, br), 7.73 (1H, dd), 7.47 (1H, t), 4.09 (3H, s), 3.92 (3H, s).

20 MP 200-201°C

Example 127

2,3-Dichloro-*N*-(6-chloro-5-(hydroxymethyl)-3-methoxypyrazin-2-yl)benzenesulphonamide



25

Prepared as for Example 120 using 3-chloro-5-{[(2,3-dichlorophenyl)sulphonyl]amino}-6-methoxypyrazine-2-carboxylic acid, methyl ester (Example 126) (0.105g). Yield 0.072g.

m/e 397, 399 ($M-1^+$, 100%)

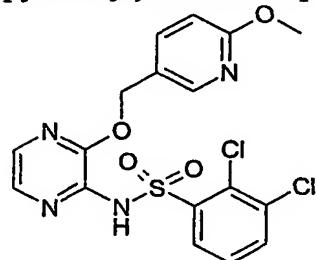
1H NMR ($CDCl_3$) δ 8.34 (1H, dd), 7.84 (1H, br), 7.74 (1H, dd), 7.45 (1H, t), 4.63 (2H, d), 4.07 (3H, s), 2.83 (1H, t).

MP 145-147°C

5

Example 128

2,3-Dichloro-N-[3-[(6-methoxy-3-pyridinyl)methoxy]-2-pyrazinyl]benzenesulphonamide



10 Prepared by the method of Example 28b using 2,3-dichloro-N-(3-chloro-2-pyrazinyl)benzenesulphonamide (Example 28a) (0.338g) and (6-methoxy-3-pyridinyl)methanol (0.21g). Yield 0.23g.

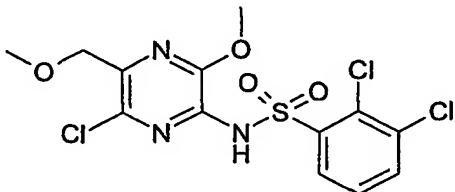
m/e 439, 440 ($M-1^+$, 100%)

15 1H NMR ($CDCl_3$) δ 8.28-8.26 (2H, m), 7.70-7.65 (3H, m), 7.60 (1H, br), 7.39 (1H, t), 6.80 (2H, d), 5.36 (2H, s), 3.97 (3H, s).

MP 187-188°C

Example 129

2,3-Dichloro-N-[6-chloro-3-methoxy-5-(methoxymethyl)-2-pyrazinyl]benzenesulphonamide



20 To a stirred solution of 2,3-dichloro-N-[6-chloro-5-(hydroxymethyl)-3-methoxy-2-pyrazinyl]benzenesulphonamide (Example 127) (0.1g) in tetrahydrofuran (3mL) was added manganese dioxide (0.131g) and the resulting suspension was stirred for 20h, filtered and concentrated. The residue was taken up into methanol (3mL) and acetic acid (0.1mL). To this solution was added ethylamine hydrochloride (0.081g) and sodium cyanoborohydride (0.051g). The resulting mixture was stirred for 20h and concentrated

onto silical gel (1 g) and eluting with methanol/dichloromethane mixtures to afford the titled compound (0.029 g) as a white solid.

m/e 412, 414 (M-1⁺, 100%)

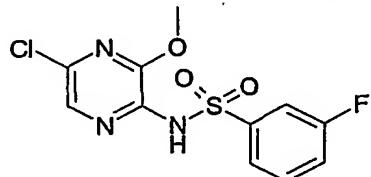
¹H NMR (CDCl₃) δ 8.35 (1H, dd), 7.72 (1H, d), 7.45 (1H, t), 4.45 (2H, s), 4.05 (3H, s), 5 3.43 (3H, s).

MP 193-196°C

Example 130

2-Chloro-N-(5-chloro-3-methoxy-2-pyrazinyl)-3-fluorobenzenesulphonamide

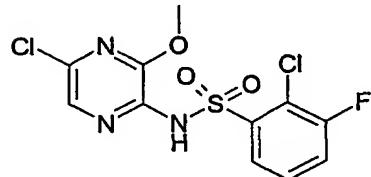
10 a) *N*-(5-Chloro-3-methoxy-2-pyrazinyl)-3-fluorobenzenesulphonamide



By the method outlined in Example 1 (reaction performed at room temperature) using 5-chloro-3-methoxy-2-pyrazinamine (0.798g) and 3-fluorobenzenesulphonyl chloride (1.17g). Yield 0.64g.

15 m/e 316 (M-1⁺, 100%)

b) 2-Chloro-*N*-(5-chloro-3-methoxy-2-pyrazinyl)-3-fluorobenzenesulphonamide.



20 A solution of *N*-(5-chloro-3-methoxy-2-pyrazinyl)-3-fluorobenzenesulphonamide (Example 130a) (0.159g) in dry tetrahydrofuran (3mL) was added to a stirred solution of lithium di-*iso*-propylamide (prepared from di-*iso*-propylamine (0.151g) and *n*-butyl lithium (2.5M in hexanes)) in tetrahydrofuran (7.0mL) at -78°C. The resulting solution was stirred at -78°C for 15 minutes and then hexachloroethane (0.472g) in tetrahydrofuran (2mL) was added and the mixture allowed to attain room temperature over a 5 hour period.

25 The reaction was quenched by the addition of 1N hydrochloric acid (10mL) and extracted into ethyl acetate (2x20mL). The combined extracts were dried (MgSO₄), filtered and concentrated to afford an oil that was purified by chromatography on silica gel eluting with ethyl acetate/*iso*-hexane mixtures gave the titled compound (0.086 g) as a white solid.

m/e 350, 352 (M-1⁺, 100%)

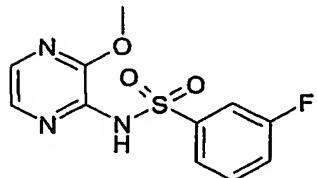
¹H NMR (CDCl₃) δ 8.16 (1H, dd), 7.81 (1H, br), 7.62 (1H, s), 7.48-7.37 (2H, m), 4.06 (3H, s)

MP 159-159.5°C

5 **Example 131**

2-Chloro-3-fluoro-N-(3-methoxy-2-pyrazinyl)benzenesulphonamide

a) 3-Fluoro-N-(3-methoxy-2-pyrazinyl)benzenesulphonamide

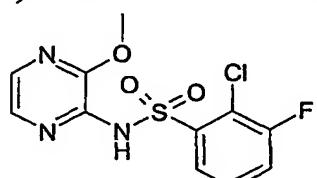


10 By the method outlined in Example 1 (reaction performed at room temperature) using 3-chloro-2-pyrazinamine (1.29g), 3-fluorobenzenesulphonyl chloride (2.13g). The crude adduct was reacted with a solution of sodium methoxide (10mL of a 25% solution in methanol) in methanol (20mL) to afford the sub-titled compound (2.36g) as a solid.

m/e 284 (M+1⁺, 100%)

15 MP 142-143°C

b) 2-Chloro-3-fluoro-N-(3-methoxy-2-pyrazinyl)benzenesulphonamide



20 Prepared as for Example 130, 3-fluoro-N-(3-methoxy-2-pyrazinyl)benzenesulphonamide (Example 131a) (0.283g), lithium di-*iso*-propylamide (prepared from di-*iso*-propylamine (0.30g) and *n*-butyl lithium (0.96mL of a 2.5M solution in hexanes)) and hexachloroethane (0.994g) in anhydrous tetrahydrofuran (20mL) afforded the titled compound (0.092g) as a white solid after re-crystallisation from *tert*-butyl methylether.

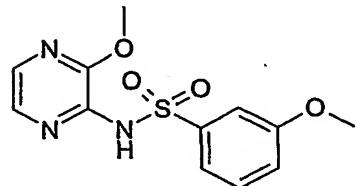
m/e 318, 320 (M-1⁺, 100%)

25 ¹H NMR (CD₃OD) δ 8.11-8.08 (2H, m), 7.57 (1H, d), 7.57-7.50 (3H, m), 4.0 (3H, s).

MP 144-145°C

Example 132

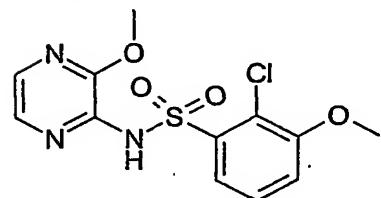
2-Chloro-3-methoxy-N-(3-methoxy-2-pyrazinyl)benzenesulphonamide

a) 3-Methoxy-*N*-(3-methoxy-2-pyrazinyl)benzenesulphonamide

By the method outlined in Example 1 (reaction performed at room temperature) using 3-chloro-2-aminopyrazine (0.83 g), 3-methoxybenzenesulfonyl chloride (1.44 g). The crude adduct was reacted with a solution of sodium methoxide (10 mL of a 25% solution in methanol) in methanol (20mL) to afford the sub-titled compound (1.41g) as a solid.

m/e 296 (M+1⁺, 100%)

MP 133-134°C

b) 2-Chloro-3-methoxy-*N*-(3-methoxypyrazin-2-yl)benzenesulphonamide

Prepared as for Example 130, 3-methoxy-*N*-(3-methoxy-2-pyrazinyl)benzenesulphonamide (Example 132a) (0.295g), lithium di-*iso*-propylamide (prepared from di-*iso*-propylamine (0.30g) and *n*-butyl lithium (0.96mL of a 2.5M solution in hexanes)) and hexachloroethane (0.994g) in anhydrous tetrahydrofuran (20mL) afforded the titled compound (0.152g) as a white solid after re-crystallisation from *tert*-butyl methylether.

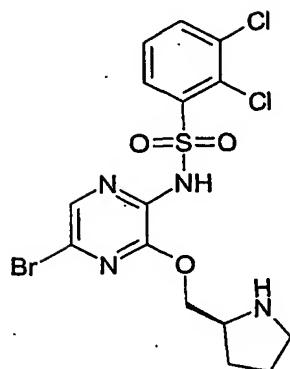
m/e 328, 329 (M-1⁺, 100%)

¹H NMR (CDCl₃) δ 7.97 (1H, d), 7.92 (1H, br), 7.65 (1H, d), 7.60 (1H, d), 7.41 (1H, t), 7.15 (1H, t), 3.99 (3H, s), 3.91 (3H, s).

MP 151-152°C

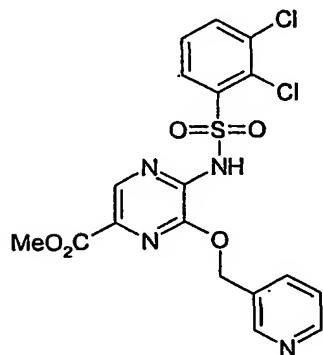
Example 133

N-[5-Bromo-3-[(2*S*)-2-pyrrolidinylmethoxy]-2-pyrazinyl]-2,3-dichlorobzenesulphonamide



Sodium hydride (0.026g of a 60% dispersion in oil) was added to a mixture of 2,3-dichloro-N-(3,5-dibromo-2-pyrazinyl)benzenesulphonamide (Example 31a) (0.1g) and 2-hydroxymethylpyrrolidine-1-carboxylic acid *tert*-butyl ester (0.088g) in 1,2-dimethoxyethane (2mL). After 0.5h, the reaction mixture was partitioned between 2N hydrochloric acid and ethyl acetate. The organic solution was dried (MgSO_4) and evaporated. Chromatography on silica gel eluting with ethyl acetate/iso-hexane mixtures gave the title compound protected with the BOC (*tert*-butoxycarbonyl) group (0.11g) as an oil. This product was dissolved in dichloromethane (6mL) and trifluoroacetic acid (2mL). After 2h, toluene was added and the solution evaporated to dryness. Crystallisation from diethyl ether gave the product as a white solid (0.083g).
 m/e 482 ($M+1^+$, 100%)
 $^1\text{H NMR}$ (D6-DMSO) δ 8.99 (1H, br), 8.65 (1H, br s), 8.13 (1H, d), 7.95 (1H, d), 7.84 (1H, s), 7.59 (1H, t), 4.57 (1H, dd), 4.39 (1H, t), 4.0 (1H, br s), 3.3 (2H, d), 2.20-2.05 (1H, m), 2.05-1.90 (2H, m), 1.85-1.75 (1H, m).
 MP 199-200°C

Example 134
5-(2,3-Dichlorobenzenesulphonylamino)-6-(3-pyridinylmethoxy)pyrazine-2-carboxylic acid, methyl ester



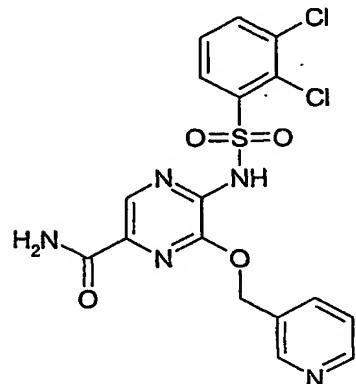
Prepared as for Example 113 using *N*-[5-bromo-3-(3-pyridinylmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide (Example 34) (0.2g) and bis(triphenylphosphine)palladium(II) dichloride (0.1g). Yield 0.14g.
m/e 469(M+1⁺, 100%)

5 ¹H NMR (D6-DMSO) δ 8.83 (1H, s), 8.61 (1H, d), 8.15-8.05 (3H,m), 7.90 (1H, d), 7.60-7.50 (2H, m), 5.48 (2H, s), 3.82(3H, s).

MP 209-210°C

Example 135

10 **5-[(2,3-Dichlorophenyl)sulphonyl]amino-6-(3-pyridinylmethoxy)-2-pyrazinecarboxamide**



15 5-(2,3-Dichlorobenzenesulphonyl)amino-6-(3-pyridinylmethoxy)pyrazine-2-carboxylic acid, methyl ester (Example 134) (0.05g) was heated at 60°C in 7M ammonia in methanol for 4 days. The solution was evaporated to dryness and the product crystallised from methyl acetate. Yield 0.027g.

m/e 453(M-1⁺, 100%)

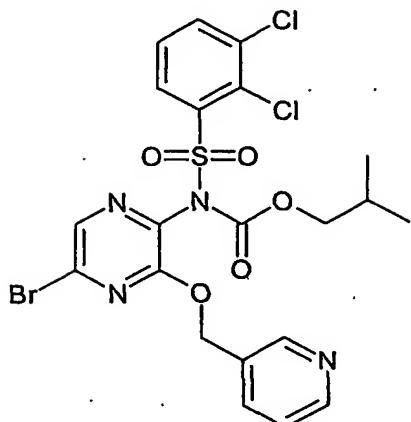
19 ¹H NMR (D6-DMSO) δ 8.72 (1H, s), 8.52 (1H, d), 7.99 (1H,d), 7.90 (1H, d), 7.83 (1H, s), 7.66 (1H, d), 7.56 (1H, s), 7.45-7.35 (2H, m), 5.49 (2H, s).

MP 174-178°C

Example 136

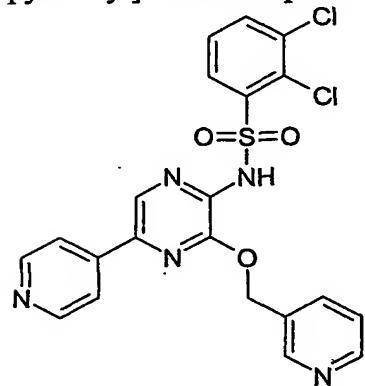
20 **2,3-Dichloro-*N*-[5-(4-pyridinyl)-3-(3-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide**

a) [5-Bromo-3-(3-pyridinylmethoxy)-2-pyrazinyl][(2,3-dichlorophenyl)sulphonyl]carbamic acid, 2-methylpropyl ester



Sodium hydride (0.045g of a 60% dispersion in oil) was added to *N*-[5-bromo-3-(3-pyridinylmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide (Example 34) (0.5g) in 1,2-dimethoxyethane (3mL). *Iso*-butylchloroformate (0.15mL) was added. After 2h, the mixture was partitioned between water and ethyl acetate. The organic layer was dried (Na₂SO₄) and evaporated to yield the product (0.65g). Used directly.

b) 2,3-Dichloro-*N*-[5-(4-pyridinyl)-3-(3-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide



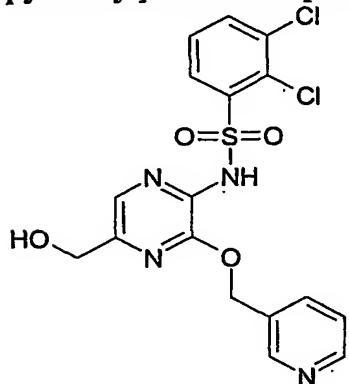
[5-Bromo-3-(3-pyridinylmethoxy)-2-pyrazinyl][(2,3-dichlorophenyl)sulphonyl]carbamic acid, 2-methylpropyl ester (Example 136a) (0.11g), 4-tributylstannanylpyridine (0.067g) and *tetrakis*(triphenylphosphine)palladium(0) (0.05g) in toluene (3mL) was heated at 95°C for 16h. Chromatography on silica gel eluting with ethyl acetate/ethanol mixtures gave the title compound protected with the 2-methylpropylcarbonyl group (0.09g). The compound was heated at 60°C in methanol (2mL) and 1M sodium hydroxide (0.36mL) for 1h. The solution was evaporated. Purification was by reverse phase preparative high pressure liquid chromatography. Yield 0.015g.

m/e 488(M+1⁺, 100%)

¹H NMR (D6-DMSO) δ 9.05 (1H, s), 8.85 (2H, d), 8.78 (1H, d), 8.62 (1H, s), 8.44-8.39 (3H, m), 8.17 (1H, dd), 7.96 (1H, dd), 7.87-7.80 (1H, m), 7.64-7.57 (1H, m), 5.74 (2H, s)
MP 210°C (dec.)

5 **Example 137**

2,3-Dichloro-N-[5-(hydroxymethyl)-3-(3-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide



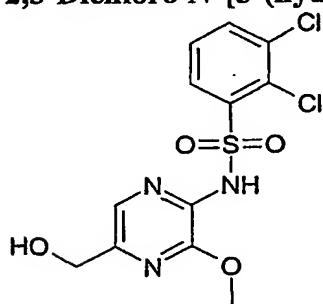
Lithium aluminium hydride (0.85mL of a 1M solution in tetrahydrofuran) was added
10 dropwise to 5-(2,3-dichlorobzenesulphonylamino)-6-(3-pyridinylmethoxy)pyrazine-2-carboxylic acid, methyl ester (Example 134) (0.2g) in tetrahydrofuran (10mL) cooled to -65°C. The reaction mixture was allowed to warm to room temperature and stirred for 1h. Aqueous acetic acid was added and the mixture extracted with ethyl acetate. The organic solution was dried (MgSO₄) and evaporated. Chromatography on silica gel eluting with
15 ethyl acetate/methanol mixtures gave the title compound (0.08g).

m/e 441(M+1⁺, 100%)

¹H NMR (D6-DMSO) δ 8.73 (1H, s), 8.55 (1H, d), 8.06 (1H, dd), 7.95-7.85 (2H, m), 7.65 (1H, s), 7.56 (1H, t); 7.64-7.57 (1H, m), 5.41 (2H, s), 5.36 (1H, t), 4.41 (2H, d)

20 **Example 138**

2,3-Dichloro-N-[5-(hydroxymethyl)-3-methoxy)-2-pyrazinyl]benzenesulphonamide



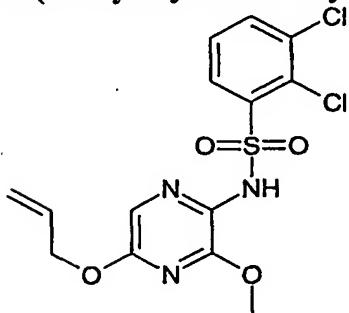
Prepared as for Example 120 using 5-(2,3-dichlorobenzenesulphonylamino)-6-methoxypyrazine-2-carboxylic acid, methyl ester (Example 113) (0.84g). Yield 0.5g. m/e 364(M+1⁺, 100%)

¹H NMR (D6-DMSO) δ 8.21 (1H, dd), 7.79 (1H, dd), 7.59 (1H, s), 7.51 (1H, t), 4.50 (2H, s), 4.01 (3H, s).

MP 160-161°C.

Example 139

N-(5-Allyloxy-3-methoxy-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide



10 Procedure as for Example 115 using *N*-(5-chloro-3-methoxy-2-pyrazinyl)-2,3-dichloro-*N*-(2-[(trimethylsilyl)oxy]ethoxy)methylbenzenesulphonamide (Example 115a) (0.25 g), allyl alcohol (0.06g) and sodium hydride (0.035g of a 60% dispersion in oil) in *N,N*-dimethylformamide (5mL) stirred at room temperature for 5 days. Purification was by 15 silica gel chromatography eluting with ethyl acetate/*iso*-hexane mixtures to give the title compound with SEM attached. Yield 0.18g. This compound was dissolved in dichloromethane (4mL) and trifluoroacetic acid (1mL). After 2h, toluene was added and the mixture evaporated to dryness. Purification was by silica gel chromatography eluting with ethyl acetate/*iso*-hexane mixtures to give the title compound. Crystallised for diethyl 20 ether/*iso*-hexane mixtures. Yield 0.026g.

m/e 390 (M+1⁺, 100%)

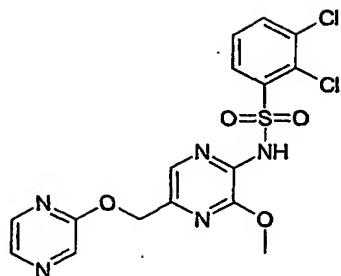
¹H NMR (D6-DMSO) δ 10.81 (1H, s), 8.0-7.9 (2H, m), 7.53 (1H, t), 7.49 (1H, s), 6.07-7.02 (1H, m), 5.38 (1H, dd), 5.26 (1H, dd), 4.80 (2H, d), 3.82 (3H, s)

MP 120-121°C

25

Example 140

2,3-Dichloro-*N*-(3-methoxy-5-[(pyrazinylmethoxy)methyl]-2-pyrazinyl)benzenesulphonamide



Sodium hydride (0.022g of a 60% dispersion in oil) was added to 2,3-dichloro-*N*-[5-(hydroxymethyl)-3-methoxy-2-pyrazinyl]benzenesulphonamide (Example 138) (0.05g) in *N*-methylpyrrolidinone (2mL). After 0.5h, chloropyrazine (0.013mL) was added and the mixture heated at 60°C for 3h. Aqueous acetic acid was added and the mixture extracted with ethyl acetate. The organic solution was dried (Na_2SO_4) and evaporated.

5

Chromatography on silica gel eluting with ethyl acetate/*iso*-hexane mixtures gave the title compound (0.012g):

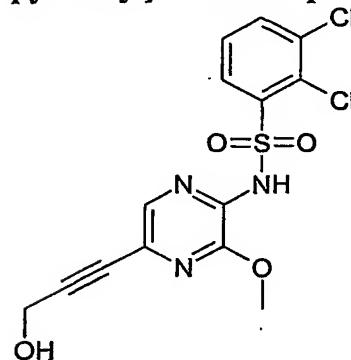
m/e 442($\text{M}+1^+$, 100%)

10 ^1H NMR (D6-DMSO) δ 8.36 (1H, s), 8.23 (2H, d), 8.06 (1H, d), 7.87 (1H, d), 7.68 (1H, s), 7.54 (1H, t), 5.26 (2H, s), 3.86 (3H, s).

MP 155°C (dec).

Example 141

15 2,3-Dichloro-*N*-[5-(3-hydroxy-1-propynyl)-3-methoxy-2-pyrazinyl]benzenesulphonamide



A mixture of *N*-(5-bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-*N*-[2-(trimethylsilyl)ethoxy]methylbenzenesulphonamide (Example 55a) (0.52g), propargyl

20 alcohol (0.223mL), copper(I)iodide (0.05g) and *bis*(triphenylphosphine)palladium(II) chloride (0.1g) in triethylamine (3mL) was stirred at room temperature and under nitrogen for 16h. The solvent was evaporated. Chromatography on silica gel eluting with ethyl acetate/*iso*-hexane mixtures gave the title compound containing the SEM ([2-(trimethylsilyl)ethoxy]methyl) protecting group (0.38g). 0.074g of this compound was

dissolved in dichloromethane (2mL) and trifluoroacetic acid (2mL). After 1h the solvent was evaporated. Chromatography on silica gel eluting with ethyl acetate/iso-hexane mixtures gave the title compound (0.043g).

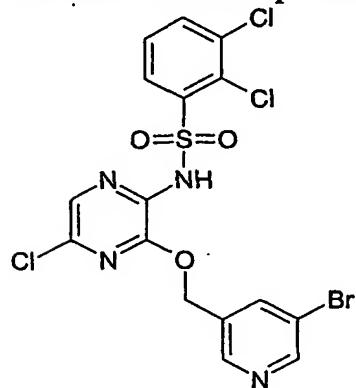
m/e 386(M-1⁺, 100%)

⁵ ¹H NMR (D6-DMSO) δ 8.07 (1H, d), 7.93 (1H, d), 7.72 (1H, s), 7.58 (1H, t), 4.29 (2H, s), 3.90 (3H, s).

Example 142

N-(3-[(5-Bromo-3-pyridinyl)methoxy]-5-chloro-2-pyrazinyl)-2,3-

¹⁰ dichlorobenzenesulphonamide



Prepared by the method of Example 31 using (5-bromo-3-pyridinyl)methanol (0.2g) and 2,3-dichloro-*N*-(3,5-dichloro-2-pyrazinyl)benzenesulphonamide (Example 74) (0.25g).

Yield 0.17g.

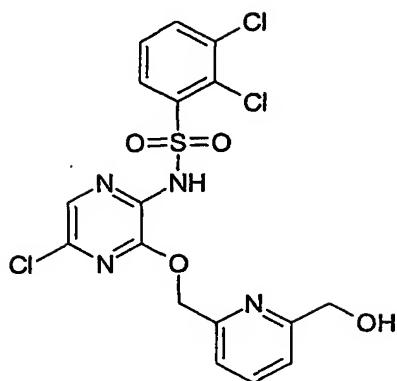
¹⁵ m/e 523(M-1⁺, 100%)

¹H NMR (D6-DMSO) δ 8.77 (1H, d), 8.71 (1H, d), 8.28 (1H, s), 8.07 (1H, dd), 7.92 (1H, d), 7.85 (1H, s), 7.55 (1H, t), 5.43 (2H, s).

MP 199-201°C .

²⁰ Example 143

2,3-Dichloro-*N*-[5-chloro-3-{{[6-(hydroxymethyl)-2-pyridinyl]methoxy}-2-pyrazinyl]benzenesulphonamide



Prepared by the method of Example 31 using 2,6-bis(hydroxymethyl)pyridine (0.11g) and 2,3-dichloro-N-(3,5-dichloro-2-pyrazinyl)benzenesulphonamide (Example 74) (0.11g) in *N*-methylpyrrolidinone (2mL). Yield 0.043g.

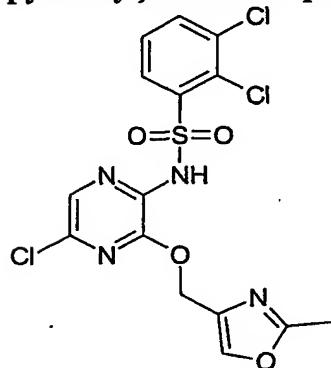
5 m/e 475(M+1⁺, 100%)

¹H NMR (D6-DMSO) δ 7.97 (1H, d), 7.83 (1H, t), 7.68 (1H, d), 7.43-7.35 (4H, m), 5.44 (1H, s), 5.32 (2H, s), 4.58 (2H, s).

MP 220°C

10 **Example 144**

2,3-Dichloro-N-{5-chloro-3-[(2-methyl-4-oxazolyl)methoxy]-2-pyrazinyl}benzenesulphonamide



Prepared by the method of Example 31b using (2-methyl-4-oxazolyl)methanol (0.08g) and

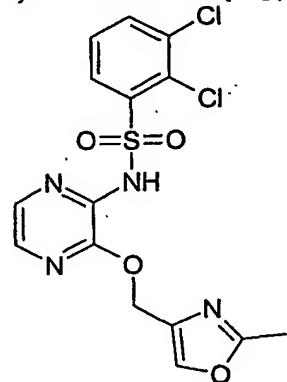
15 2,3-dichloro-N-(3,5-dichloro-2-pyrazinyl)benzenesulphonamide (Example 74) (0.26g).

Yield 0.083g.

m/e 449(M+1⁺, 100%)

¹H NMR (D6-DMSO) δ 8.09 (1H, s), 8.03 (1H, dd), 7.94 (1H, dd), 7.85 (1H, s), 7.55 (1H, t), 5.23 (2H, s), 2.45 (3H, s)

20 MP 172-173°C.

Example 145**2,3-Dichloro-N-{3-[(2-methyl-4-oxazolyl)methoxy]-2-pyrazinyl}benzenesulphonamide**

Prepared by the method of Example 28 using (2-methyl-4-oxazolyl)methanol (0.3g) and

5 2,3-dichloro-N-(3-chloro-2-pyrazinyl)benzenesulphonamide (0.89g). Yield 0.035g.

m/e 412(M-1⁺, 100%)

¹H NMR (D6-DMSO) δ 8.06 (2H, dd), 7.92 (1H, dd), 7.85 (1H, br s), 7.70 (1H, br s), 7.56 (1H, t), 5.23 (2H, s), 2.41 (3H, s).

MP 207-209°C.

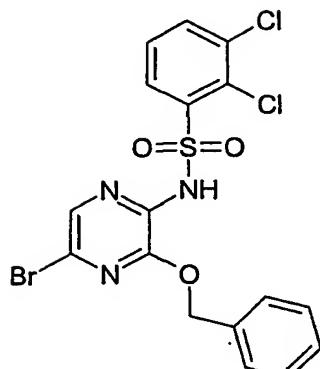
10

Examples 146-165 were prepared using the following procedure:

To a solution of *N*-(3,5-dibromo-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide (Example 31) (0.003g) and primary alcohol (0.026mL of a 0.5M solution in *N*-methylpyrrolidinone) in *N*-methylpyrrolidinone (0.1mL) was added potassium *tert*-butoxide (0.050mL of a 1M solution in tetrahydrofuran). The solution was allowed to stand for 24 hours. The reaction mixture was diluted with acetic acid (0.010mL) and water (0.10mL) and the solvents were evaporated. The residue was redissolved in dimethylsulphoxide (0.5mL) and purified by mass directed high pressure liquid chromatography. The solvent was evaporated to afford a solid.

15

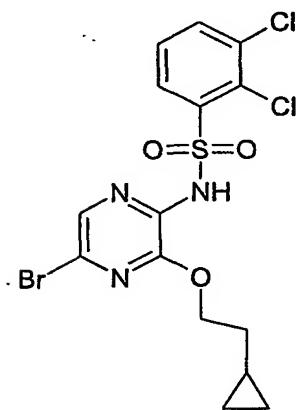
Example 146***N*-[5-Bromo-3-(phenylmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide**



m/e 489(M+1⁺, 100%)

Example 147

5 *N*-[5-Bromo-3-(2-cyclopropylethoxy)pyrazinyl]-2,3-dichlorobenzenesulphonamide

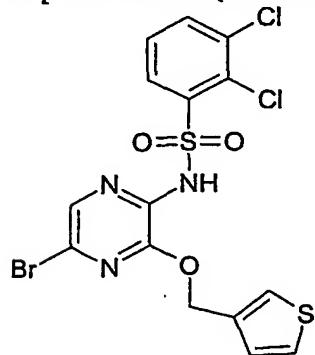


m/e 467(M+1⁺, 100%)

10

Example 148

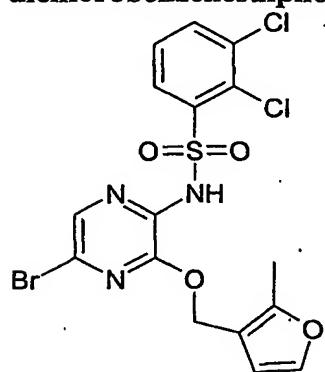
N-[5-Bromo-3-(3-thienylmethoxy)pyrazinyl]-2,3-dichlorobenzenesulphonamide



m/e 495(M+1⁺, 100%)

Example 149

N-(5-Bromo-3-[(2-methyl-3-furanyl)methoxy]-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide

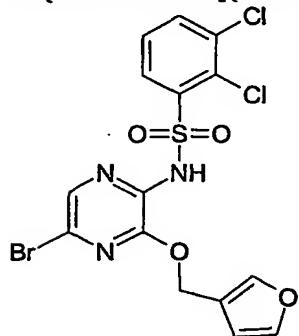


m/e 493(M+1⁺, 100%)

10

Example 150

N-(5-Bromo-3-[(3-furanyl)methoxy]-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide

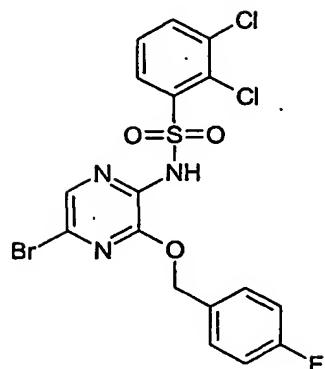


m/e 479(M+1⁺, 100%)

15

Example 151

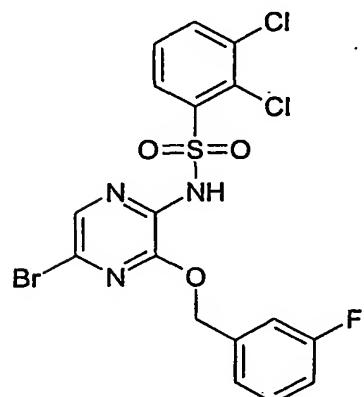
N-(5-Bromo-3-[(4-fluorophenyl)methoxy]-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide



m/e 507(M+1⁺, 100%)

Example 152

5 *N*-(5-Bromo-3-[(3-fluorophenyl)methoxy]-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide

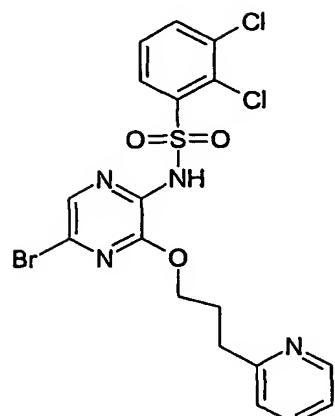


m/e 507(M+1⁺, 100%)

10

Example 153

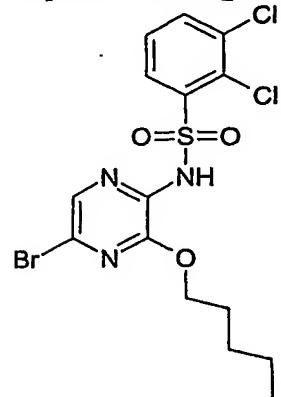
N-(5-Bromo-3-[3-(2-pyridinyl)propoxy]-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide



m/e 518(M+1⁺, 100%)

Example 154

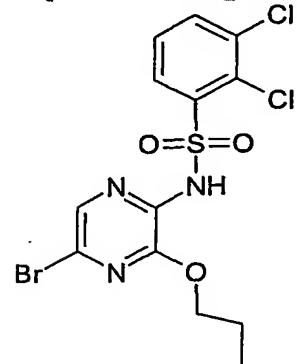
5 **N-[5-Bromo-3-(pentyloxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide**



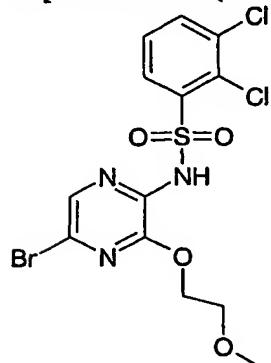
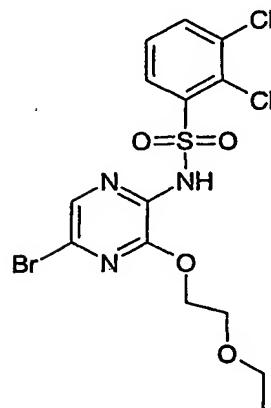
m/e 469(M+1⁺, 100%)

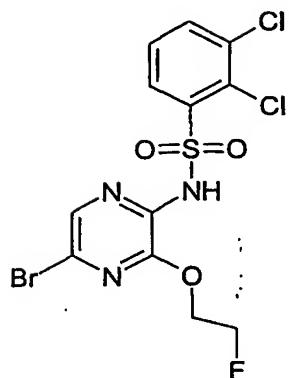
Example 155

10 **N-[5-Bromo-3-(propyloxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide**



m/e 441(M+1⁺, 100%)

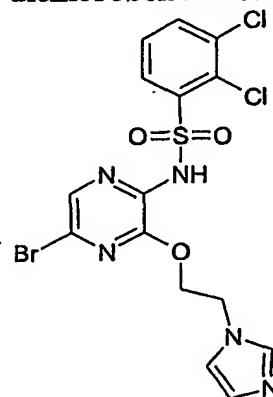
Example 156*N*-[5-Bromo-3-(2-methoxyethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide5 m/e 457($M+1^+$, 100%)**Example 157***N*-[5-Bromo-3-(2-ethoxyethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide10 m/e 471($M+1^+$, 100%)**Example 158***N*-[5-Bromo-3-(2-fluoroethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide



m/e 445(M+1⁺, 100%)

Example 159

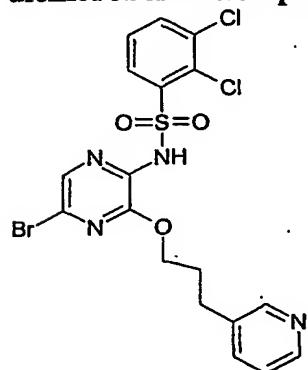
5 *N*-(5-Bromo-3-[2-(1*H*-imidazol-1-yl)ethoxy]-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide



m/e 493(M+1⁺, 100%)

10 **Example 160**

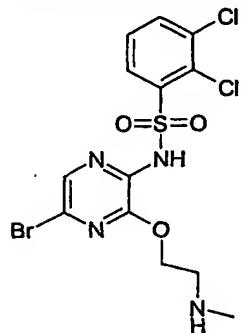
N-(5-Bromo-3-[3-(3-pyridinyl)propoxy]-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide



m/e 516(M-1⁺, 100%)

Example 161

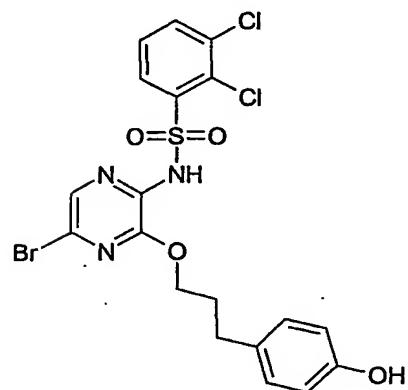
N-[5-Bromo-3-[2-(methylamino)ethoxy]-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide



m/e 456(M+1⁺, 100%)

Example 162

N-{5-Bromo-3-[3-(4-hydroxyphenyl)propoxy]-2-pyrazinyl}-2,3-dichlorobenzenesulphonamide

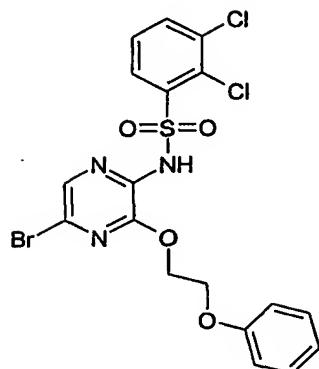


m/e 533(M+1⁺, 100%)

15

Example 163

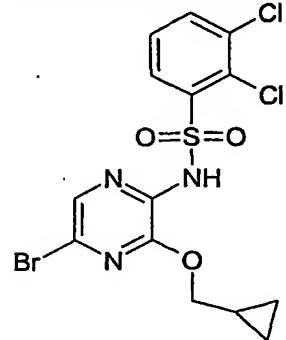
N-[5-Bromo-3-(2-phenoxyethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide



m/e 517(M-1⁺, 100%)

Example 164

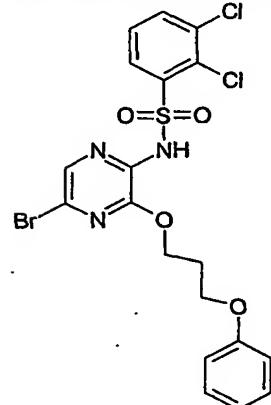
5 *N*-[5-Bromo-3-(cyclopropylmethoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide



m/e 453(M+1⁺, 100%)

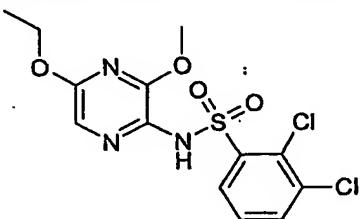
Example 165

10 *N*-[5-Bromo-3-(3-phenoxypropoxy)-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide



m/e 531(M-1⁺, 100%)

Example 166

2,3-Dichloro-N-(5-ethoxy-3-methoxy-2-pyrazinyl)benzenesulphonamide

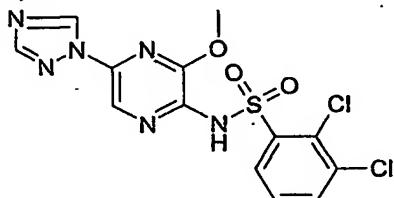
Prepared as for Example 56 using *N*-(5-bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-*N*-[{2-(trimethylsilyl)ethoxy}methyl]benzenesulphonamide (Example 55a) (0.3g) and sodium ethoxide (5mL of a 0.5M solution in ethanol). Yield 0.1g.

m/e 378 (M+1,100%)

¹H NMR (CDCl₃) δ 8.22 (1H, d), 7.65 (1H, d), 7.49 (1H, s), 7.34 (1H, t), 7.30 (1H, s), 4.24 (2H, q), 3.95 (3H, s), 1.36 (3H, t)

MP 96-97°C

10

Example 167**2,3-Dichloro-N-[3-methoxy-5-([1,2,4]-1-triazolyl)-2-pyrazinyl]benzenesulphonamide**

Prepared as for Example 101b (reaction heated at 50°C) using *N*-(5-bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-*N*-[{2-(trimethylsilyl)ethoxy}methyl]benzenesulphonamide (Example 55a) (0.25g) and [1,2,4]triazole (0.1g). The intermediate product containing the SEM (2-[trimethylsilyl]ethoxymethyl) group was purified by silica gel chromatography eluting with ethyl acetate/iso-hexane mixtures. Deprotection as for Example 101b gave the title compound. Yield 0.035g.

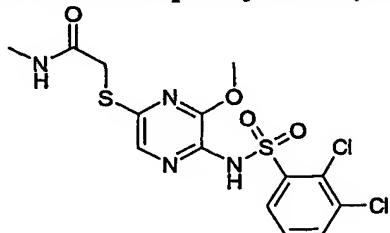
20 m/e 401 (M+1⁺, 100%)

¹H NMR (CDCl₃) δ 8.92 (1H, s), 8.34 (1H, d), 8.24 (1H, s), 8.08 (1H, s), 8.01 (1H, br s), 7.72 (1H, d), 7.43 (1H, t), 4.14 (3H, t)

MP 248-249°C

25 **Example 168**

2-[5-(2,3-Dichlorobenzenesulphonylamino)-6-methoxy-2-pyrazinylsulphonyl]-N-



methylacetamide

Prepared as for Example 101b using *N*-(5-bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-*N*-[{2-(trimethylsilyl)ethoxy}methyl]benzenesulphonamide (Example 55a) (0.4g) and 2-mercaptop-*N*-methylacetamide (0.1g). The intermediate product containing the SEM (2-[trimethylsilyl]ethoxymethyl) group was purified by silica gel chromatography eluting with ethyl acetate/iso-hexane mixtures. Deprotection as for Example 101b gave the title compound. Yield 0.05g.

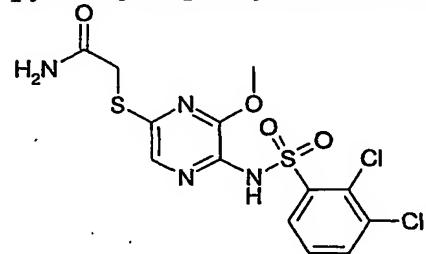
m/e 437 (M+1⁺, 100%)

¹⁰ ¹H NMR (CDCl₃) δ 8.25 (1H, dd), 7.76 (1H, s), 7.68 (1H, dd), 7.58 (1H, s), 7.40 (1H, t), 6.62 (1H, br s), 3.99 (3H, s), 3.69 (2H, s), 2.86 (3H, d)

MP 150-152°C

Example 169

¹⁵ 2-[5-(2,3-Dichlorobenzenesulphonylamino)-6-methoxy-2-pyrazinylsulphonyl]acetamide

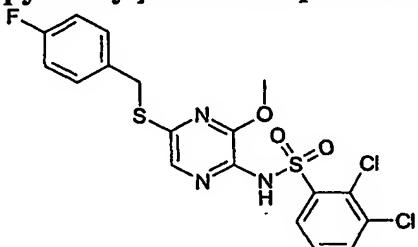


Prepared as for Example 101b using *N*-(5-bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-*N*-[{2-(trimethylsilyl)ethoxy}methyl]benzenesulphonamide (Example 55a) (0.2g) and 2-mercaptopacetamide (0.05g). The intermediate product containing the SEM group was purified by silica gel chromatography eluting with ethyl acetate/iso-hexane mixtures. Deprotection as for Example 101b gave the title compound. Yield 0.03g.

m/e 423 (M+1⁺, 100%)

¹⁶ ¹H NMR (CDCl₃) δ 7.98 (1H, dd), 7.75 (1H, d), 7.46-7.42 (3H, m), 7.06 (1H, s), 3.83 (3H, s), 2.59 (2H, s)

MP 163-164°C

Example 170**2,3-Dichloro-N-[5-(4-fluorobenzylsulphonyl)-3-methoxy-2-pyrazinyl]benzenesulphonamide**

5 Prepared as for Example 101b using *N*-(5-bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-*N*-{(2-(trimethylsilanyl)ethoxy)methyl}benzenesulphonamide (Example 55a) (0.4g) and (4-fluorophenyl)methanethiol (0.13g). The intermediate product containing the SEM group was purified by silica gel chromatography eluting with ethyl acetate/iso-hexane mixtures.

Deprotection as for Example 101b gave the title compound. Yield 0.2g

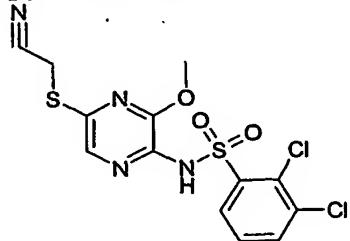
10 m/e 474 (M+1⁺, 100%)

¹H NMR (CDCl₃) δ 8.25 (1H, dd), 7.73 (1H, s), 7.67 (1H, dd), 7.51 (1H, s), 7.38 (1H, t), 7.27 (2H, m), 6.92 (2H, m), 4.24 (2H, s), 4.01 (3H, s)

MP 119-120°C

15 **Example 171**

2,3-Dichloro-N-[5-cyanomethylsulphonyl-3-methoxy-2-pyrazinyl]benzenesulphonamide



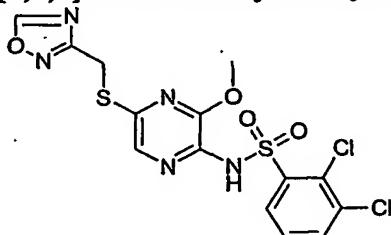
See example 172 for preparation.

20 m/e 403 (M-1⁺, 100%)

¹H NMR (CDCl₃) δ 8.28 (1H, dd), 7.84 (1H, s), 7.69 (1H, dd), 7.63 (1H, s), 7.38 (1H, t), 4.11 (3H, s), 3.78 (2H, s)

MP 158-159°C

25 **Example 172**

2,3-Dichloro-*N*-[3-methoxy-5-([1,2,4]-3-oxadiazolylmethylsulphonyl)-2-pyrazinyl]benzenesulphonamide

pyrazinyl]benzenesulphonamide

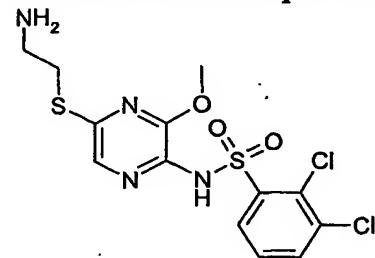
Prepared as for Example 101b using *N*-(5-bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-*N*-[{2-(trimethylsilyl)ethoxy}methyl]benzenesulphonamide (Example 55a) (0.4g), [1,2,4]-3-oxadiazolylmethanethiol (0.15g) and cesium carbonate (0.5g) at room temperature for 16h. The intermediate products containing the SEM (2-[trimethylsilyl]ethoxymethyl) group was purified by silica gel chromatography eluting with ethyl acetate/iso-hexane mixtures. Deprotection as for Example 101b gave the title compound (0.09g) and 2,3-dichloro-*N*-[5-cyanomethylsulphonyl-3-methoxy-2-pyrazinyl]benzenesulphonamide (Example 171) (0.1g) which were separated by silica gel chromatography eluting with dichloromethane.

m/e 448 (M+1⁺, 100%)

¹H NMR (CDCl₃) δ 8.64 (1H, s), 8.26 (1H, dd), 7.76 (1H, s), 7.67 (1H, dd), 7.57 (1H, s), 7.37 (1H, t), 4.39 (2H, s), 4.04 (3H, s)

MP 154-156°C

Example 173

N-[5-(2-Aminoethylsulphonyl)-3-methoxy-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide

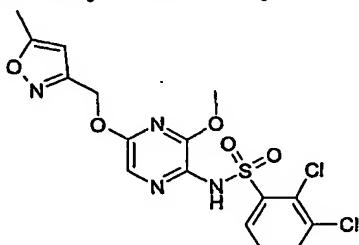
20

Prepared as for Example 101b using *N*-(5-bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-*N*-[{2-(trimethylsilyl)ethoxy}methyl]benzenesulphonamide (Example 55a) (0.45g) and 2-aminoethanethiol hydrochloride (0.2g). Yield 0.03g

m/e 409 (M+1⁺, 100%)

¹H NMR (D6-DMSO) δ 8.02 (1H, dd), 7.94 (1H, dd), 7.87 (1H, s), 7.70 (1H, s), 7.58 (1H, t), 3.93 (3H, s), 3.48 (2H, br s), 3.28 (2H, t), 3.10-3.03 (2H, m)

MP 189-190°C

Example 174**2,3-Dichloro-N-[3-methoxy-5-(5-methyl-3-isoxazolylmethoxy))-2-****5 pyrazinyl]benzenesulphonamide**

Prepared as for Example 115b using *N*-(5-bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-*N*[(2-(trimethylsilyl)ethoxy)methyl]benzenesulphonamide (Example 55a) (0.3g) and (5-methyl-3-isoxazolyl)methanol (0.13g). The intermediate product containing the SEM (2-(trimethylsilyl)ethoxymethyl) group was purified by silica gel chromatography eluting with ethyl acetate/iso-hexane mixtures. Deprotection as for Example 115b gave the title compound. Yield 0.2g

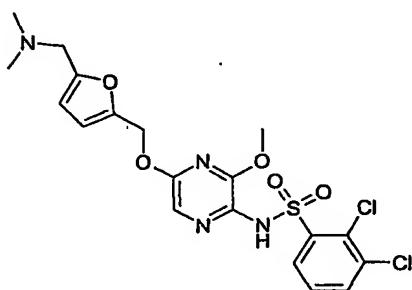
m/e 445 (M+1⁺, 100%)

¹H NMR (CDCl₃) δ 8.22 (1H, dd), 7.66 (1H, dd), 7.59 (1H, s), 7.38 (2H, t), 6.01 (1H, t), 5.31 (2H, s), 3.97 (3H, s), 2.43 (3H, s)

15 MP 142-143°C

Example 175**2,3-Dichloro-N-[5-(5-dimethylaminomethyl-2-furanylmethoxy)-3-methoxy-2-pyrazinyl]benzenesulphonamide**

20



Prepared as for Example 115b using *N*-(5-bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-*N*[(2-(trimethylsilyl)ethoxy)methyl]benzenesulphonamide (Example 55a) (0.3g) and (5-dimethylaminomethyl-2-furanylmethanol (0.2g). After removal of the SEM (2-(trimethylsilyl)ethoxymethyl) group the title compound was purified by silica gel chromatography eluting with methanol/dichloromethane mixtures Yield 0.23g

m/e 487 ($M+1^+$, 100%)

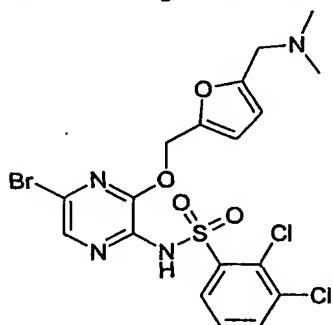
^1H NMR (CDCl_3) δ 8.21 (1H, dd), 7.66 (1H, dd), 7.37 (2H, t), 6.39 (2H, s), 5.20 (2H, s), 4.00 (3H, s), 3.84 (2H, s), 2.51 (6H, s)

MP 114-115°C

5

Example 176

N-(5-Bromo-3-(5-dimethylaminomethyl-2-furanylmethoxy)-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide



10 Prepared by the method of Example 31 using (5-dimethylaminomethyl-2-furanyl)methanol (0.2g) and 2,3-dichloro-*N*-(3,5-dibromo-2-pyrazinyl)benzenesulphonamide (Example 31a) (0.2g). Purified by silica gel chromatography eluting with methanol/dichloromethane mixtures and recrystallised from acetonitrile. Yield 0.058g.

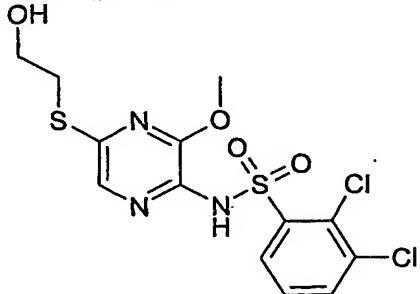
m/e 535 ($M+1^+$, 100%)

15 ^1H NMR ($\text{D}_6\text{-DMSO}$) δ 7.92 (1H, dd), 7.63 (1H, dd), 7.36 (2H, t), 6.71 (1H, d), 6.68 (1H, d), 5.22 (2H, s), 4.37 (2H, d), 2.75 (6H, s)

MP 206-207°C

Example 177

20 2,3-Dichloro-*N*-(5-(2-hydroxyethylsulphanyl)-3-methoxy-2-



pyrazinyl]benzenesulphonamide

Prepared as for Example 101b using *N*-(5-bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-*N*[(2-(trimethylsilyl)ethoxy)methyl]benzenesulphonamide (Example 55a) (0.2g) and 2-mercaptopropanol (0.2g). After removal of the SEM (2-[trimethylsilyl]ethoxymethyl) group

the title compound was purified by silica gel chromatography eluting with methanol/dichloromethane mixtures. Yield 0.015g
 m/e 410 (M+1⁺, 100%)

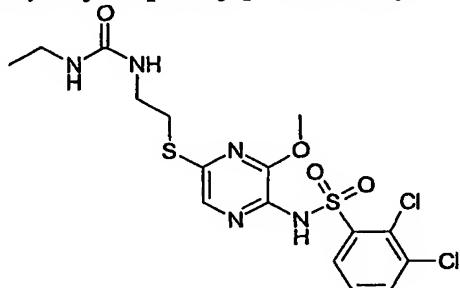
¹H NMR (CDCl₃) δ 8.27 (1H, dd), 7.78 (1H, s), 7.67 (1H, dd), 7.61 (1H, s), 7.39 (1H, t),

5 4.04 (3H, s), 3.83 (2H, t), 3.24 (2H, t)

MP 180-181°C

Example 178

2,3-Dichloro-N-[5-[2-(ethylureido)ethylsulphanyl]-3-methoxy-2-



10 pyrazinyl]benzenesulphonamide

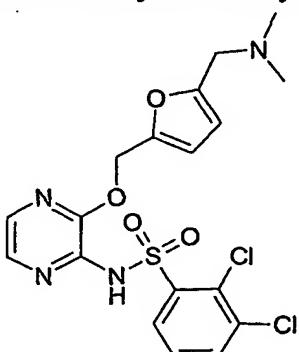
Ethylisocyanate (0.016g) was added to *N*-[5-(2-aminoethylsulphanyl)-3-methoxy-2-pyrazinyl]-2,3-dichloro-benzenesulphonamide (Example 173) (0.08g) in dichloromethane (5mL). After 1h, the reaction mixture was evaporated to dryness. Purified by silica gel chromatography eluting with methanol/dichloromethane mixtures. Yield 0.015g.

15 m/e 480 (M+1⁺, 100%)

¹H NMR (CDCl₃) δ 8.27 (1H, dd), 7.69 (1H, dd), 7.56 (1H, s), 7.39 (1H, t), 4.60 (1H, br s), 4.18 (1H, br s), 4.04 (3H, s), 3.40-3.30 (2H, m), 3.30-3.2 (2H, m), 3.25-3.20 (2H, m), 1.15 (3H, t)

Example 179

2,3-Dichloro-N-[3-(5-dimethylaminomethyl-2-furanylmethoxy)-2-



pyrazinyl]benzenesulphonamide

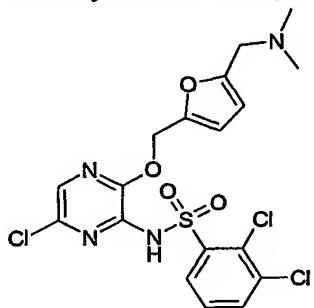
Prepared by the method of Example 28 using (5-dimethylaminomethyl-2-furanyl)methanol (0.2g) and 2,3-dichloro-N-(3-chloro-2-pyrazinyl)benzenesulphonamide (Example 28) (0.4g). Purified by silica gel chromatography eluting with methanol/dichloromethane mixtures. Yield 0.2g.

5 m/e 455 (M-1⁺, 100%)

¹H NMR (D6-DMSO) δ 7.96 (1H, dd), 7.66 (1H, dd), 7.40 (1H, t), 7.30 (1H, d), 7.24 (1H, d), 6.65 (1H, s), 6.64 (1H, d), 5.23 (2H, s), 4.25 (2H, s), 2.66 (6H, s)

Example 180

10 **2,3-Dichloro-N-[6-chloro-3-(5-dimethylaminomethyl-2-furanylmethoxy)-2-**



pyrazinyl]benzenesulphonamide

Prepared by the method of Example 31 using (5-dimethylaminomethyl-2-furanyl)methanol (0.2g) and *N*-(3-bromo-6-chloro-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide (Example 98) (0.3g). Purified by silica gel chromatography eluting with methanol/dichloromethane

15 mixtures. Yield 0.11g.

m/e 491 (M+1⁺, 100%)

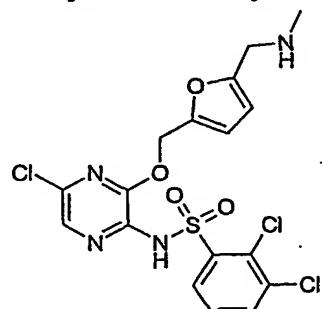
¹H NMR (D6-DMSO) δ 8.01 (1H, dd), 7.66 (1H, dd), 7.39 (1H, t), 7.11 (1H, s), 6.69 (1H, d), 6.67 (1H, d), 5.20 (2H, s), 4.39 (2H, s), 2.76 (6H, s)

MP 209-210°C

20

Example 181

2,3-Dichloro-N-[6-chloro-3-(5-methylaminomethyl-2-furanylmethoxy)-2-



pyrazinyl]benzenesulphonamide

Prepared by the method of Example 31 using (5-methylaminomethyl-2-furanyl)methanol (0.3g) and 2,3-dichloro-N-(3,5-dichloro-2-pyrazinyl)benzenesulphonamide (Example 74) (0.4g). Purified by silica gel chromatography eluting with methanol/dichloromethane mixtures. Yield 0.03g.

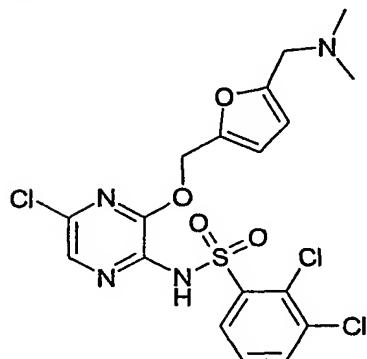
5 m/e 477 ($M+1^+$, 100%)

1 H NMR (D6-DMSO) δ 8.98 (2H, br), 7.92 (1H, d), 7.63 (1H, d), 7.35 (1H, t), 7.29 (1H, s), 6.67 (1H, d), 6.64 (1H, d), 5.20 (2H, s), 4.25 (2H, s), 2.59 (3H, s)

MP 211-212°C

10 **Example 182**

2,3-Dichloro-N-[5-chloro-3-(5-dimethylaminomethyl-2-furanylmethoxy)-2-pyrazinyl]benzenesulphonamide



Prepared by the method of Example 31 using (5-dimethylaminomethyl-2-furanyl)methanol (0.3g) and 2,3-dichloro-N-(3,5-dichloro-2-pyrazinyl)benzenesulphonamide (Example 74) (0.4g). Purified by silica gel chromatography eluting with methanol/dichloromethane mixtures. Yield 0.30g.

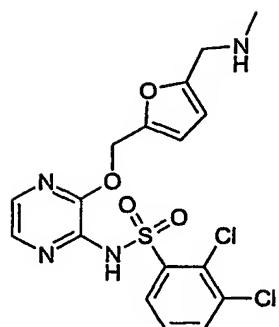
15 m/e 491 ($M+1^+$, 100%)

1 H NMR (D6-DMSO) δ 7.93 (1H, dd), 7.65 (1H, dd), 7.36 (1H, t), 7.32 (1H, s), 6.71 (1H, d), 6.69 (1H, d), 5.23 (2H, s), 4.38 (2H, s), 2.75 (6H, s)

20 MP 209-210°C

Example 183

2,3-Dichloro-N-[3-(5-methylaminomethyl-2-furanylmethoxy)-2-pyrazinyl]benzenesulphonamide



Prepared by the method of Example 28 using (5-methylaminomethyl-2-furanyl)methanol (0.2g) and 2,3-dichloro-*N*-(3-chloro-2-pyrazinyl)benzenesulphonamide (Example 28) (0.4g). Purified by silica gel chromatography eluting with methanol/dichloromethane mixtures. Yield 0.12g.

m/e 443 (M+1⁺, 100%)

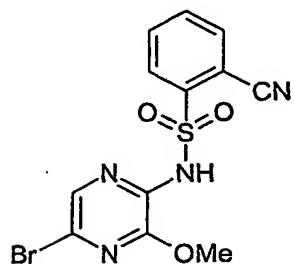
¹H NMR (D6-DMSO) δ 8.99 (2H, br s), 7.95 (1H, d), 7.62 (1H, d), 7.35 (1H, t), 7.24 (1H, d), 7.15 (1H, d), 6.88 (1H, d), 6.63 (1H, d), 5.20 (2H, s), 4.24 (2H, s), 2.58 (3H, s)

MP 198-199°C

10

Example 184

N-(5-Bromo-3-methoxypyrazinyl)-2-cyanobenzenesulphonamide



15

Prepared by the method of Example 1 (reaction performed at room temperature) using 5-bromo-3-methoxy-2-pyrazinamine (0.2g) and 2-cyanobenzenesulphonyl chloride (0.24g). Yield 0.059g.

m/e 369/370 (M+1⁺), 307/309 (100%)

20 ¹H NMR (D6-DMSO) δ 8.14 (1H, d), 8.09 (1H, d), 7.93-7.82 (3H, m), 3.93 (3H, s).

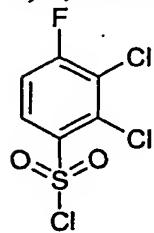
MP 190-191.5°C

Example 185

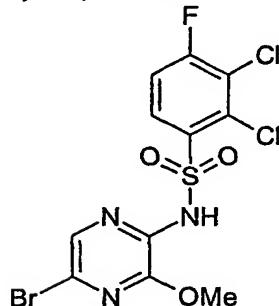
N-(5-Bromo-3-methoxypyrazinyl)-2,3-dichloro-4-fluorobenzenesulphonamide

25

a) 2,3-Dichloro-4-fluorobenzenesulphonyl chloride



Chlorosulphonic acid (12.1mL) was added dropwise to a solution of 2,3-dichloro-4-fluorobenzene (5.0g) in dichloromethane (12mL) at -40°C. The solution was allowed to slowly warm to room temperature and was stirred for 3 days. The solution was poured onto crushed ice/water, extracted into dichloromethane and concentrated under reduced pressure. Purified by silica gel chromatography eluting with dichloromethane/*iso*-hexane mixtures. Yield 4.2g
 m/e 262/264 (M⁺), 163 (100%).

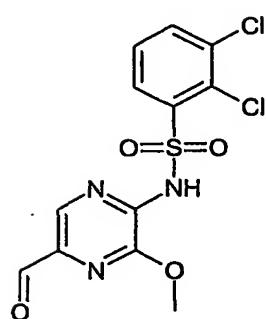
b) *N*-(5-Bromo-3-methoxypyrazinyl)-2,3-dichloro-4-fluorobenzenesulphonamide

Prepared by the method of Example 1 (reaction performed at room temperature) using 5-bromo-3-methoxy-2-pyrazinamine (0.2g) and 2,3-dichloro-4-fluorobenzenesulphonyl chloride (Example 185a) (0.31g). Yield 0.042g.
 m/e 430 (M-1, 100%)
¹H NMR (D6-DMSO) δ 8.16-8.12 (1H, m), 7.81 (1H, s), 7.68-7.64 (1H, m), 3.92 (3H, s).
 MP 208-211°C

20

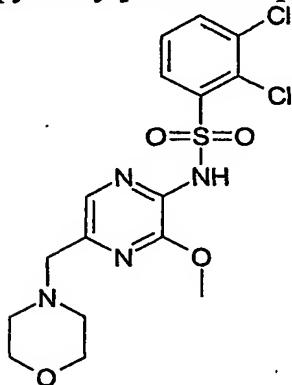
Example 186**2,3-Dichloro-*N*-(3-methoxy-5-(4-morpholinylmethyl)-2-pyrazinyl)benzenesulphonamide**

25 a) 2,3-Dichloro-*N*-(5-formyl-3-methoxy-2-pyrazinyl)benzenesulphonamide



Prepared as for Example 107a using 2,3-dichloro-*N*-[5-(hydroxymethyl)-3-methoxy-2-pyrazinyl]benzenesulphonamide (Example 138) (0.6g). Yield 0.53g. Used directly.

5 b) 2,3-Dichloro-*N*-[3-methoxy-5-(4-morpholinylmethyl)-2-pyrazinyl]benzenesulphonamide



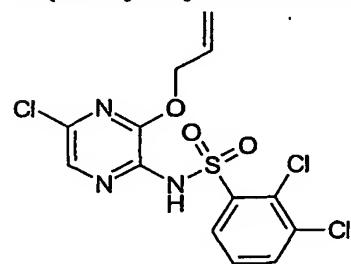
Prepared as for Example 107b using 2,3-dichloro-*N*-(5-formyl-3-methoxy-2-pyrazinyl)benzenesulphonamide (Example 186a) (0.26g) and morpholine (3.7mL). Yield 10 0.057g.

m/e 433 (M+1⁺, 100%)

¹H NMR (D6-DMSO) δ 8.12 (1H, d), 7.94 (1H, d), 7.59 (1H, t), 4.20 (2H, s), 3.96 (3H, s), 3.85-3.65 (5H, m)

15 **Example 187**

N-(3-Allyloxy-5-chloro-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide



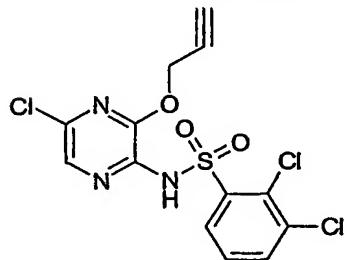
Prepared by the method of Example 31 using allyl alcohol (10mL) as solvent and 2,3-dichloro-*N*-(3,5-dichloro-2-pyrazinyl)benzenesulphonamide (Example 74) (0.35g). Yield 0.32g.

m/e 393 (M-1⁺, 100%)

¹H NMR (D6-DMSO) δ 11.80 (1H, br s), 8.08 (1H, dd), 7.96 (1H, dd), 7.82 (1H, dd), 7.58 (1H, t), 6.10-6.00 (1H, m), 5.49 (1H, dddd), 5.29 (1H, dddd), 4.86 (2H, dddd)
MP 145-146°C

Example 188

¹⁰ 2,3-Dichloro-*N*-[5-chloro-3-(2-propynyoxy)-2-pyrazinyl]benzenesulphonamide



Prepared by the method of Example 31 using propargyl alcohol (0.3g) and 2,3-dichloro-*N*-(3,5-dichloro-2-pyrazinyl)benzenesulphonamide (Example 74) (0.35g). Yield 0.2g.

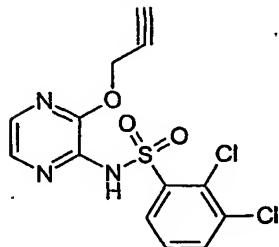
m/e 390 (M-1⁺, 100%)

¹⁵ ¹H NMR (D6-DMSO) δ 8.08 (1H, dd), 7.95 (1H, dd), 7.86 (1H, s), 7.58 (1H, t), 5.02 (2H, d), 3.65 (1H, t)

MP 138-139°C

Example 189

²⁰ 2,3-Dichloro-*N*-[3-(2-propynyoxy)-2-pyrazinyl]benzenesulphonamide



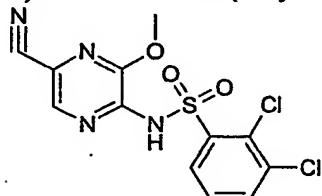
Prepared by the method of Example 28 using propargyl alcohol as solvent (3mL), 2,3-dichloro-*N*-(3-chloro-2-pyrazinyl)benzenesulphonamide (Example 28) (0.3g) and sodium hydride (0.2g of a 60% dispersion in oil) at room temperature for 16h. Yield 0.27g.

²⁵ m/e 356 (M-1⁺, 100%)

¹H NMR (D6-DMSO) δ 11.67 (1H, br s), 8.10 (1H, dd), 7.94 (1H, dd), 7.85 (1H, br), 7.72 (1H, br), 7.59 (1H, t), 5.01 (2H, d), 3.56 (1H, t)
 MP 153-154°C

5 **Example 190**

2,3-Dichloro-N-(5-cyano-3-methoxy-2-pyrazinyl)benzenesulphonamide



Prepared as for Example 78 using *N*-(5-bromo-3-methoxy-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide (Example 8) (0.1g). Yield 0.034g.

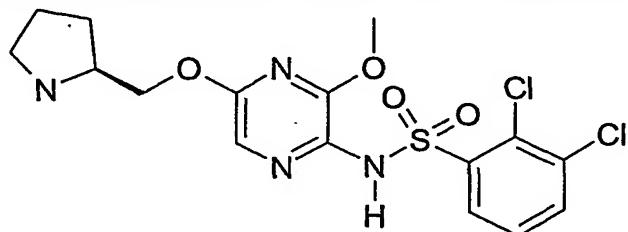
10 m/e 357 (M-1⁺, 100%)

¹H NMR (D6-DMSO) δ 8.15 (1H, s), 8.14 (1H, dd), 7.95 (1H, dd), 7.59 (1H, t), 3.96 (3H, s)

MP 239-240°C

15 **Example 191**

2,3-Dichloro-N-{3-methoxy-5-[(2S)-pyrrolidin-2-ylmethoxy]-2-pyrazinyl}benzenesulfonamide hydrochloride

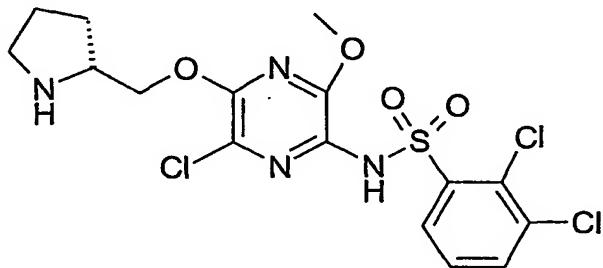


Procedure as for Example 115 using *N*-(5-bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-*N*-{(2-[(trimethylsilyl)oxy]ethoxy}methyl)benzenesulphonamide (Example 55a) (0.5 g), *tert*-butyl (2S)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (0.603 g) and sodium hydride (0.12g of a 60% dispersion in oil) in *N*-methylpyrrolidinone (20mL). The adduct was deprotected with HCl (4M in dioxane) to afford the titled adduct (0.241g) as a white solid.
 m/e 433, 435 (M-HCl+1⁺, 100%)

25 ¹H NMR (D6-DMSO) δ 10.92 (1H, s), 9.45 (1H, br), 8.93 (1H, br), 7.98 (1H, d), 7.93 (1H, d), 7.57 (1H, d), 7.52 (1H, d), 4.53 (1H, dd), 4.37 (1H, dd), 3.94-3.86 (1H, m), 3.85 (3H, s), 3.22-3.18 (2H, m), 2.13-2.08 (1H, m), 1.99-1.86 (2H, m), 1.76-1.67 (1H, m).

Example 192

5 **2,3-Dichloro-N-{6-chloro-3-methoxy-5-[(2R)-2-pyrrolidinylmethoxy]-2-pyrazinyl}benzenesulphonamide Hydrochloride**



10 Procedure as for Example 115 using 2,3-dichloro-N-(5,6-dichloro-3-methoxy-2-pyrazinyl)-
 15 *N*-{[2-(trimethylsilyl)ethoxy]methyl}benzenesulphonamide (Example 66a) (0.29g), *tert*-
 butyl (2*S*)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (0.15 g) and sodium hydride
 (0.04g of a 60% dispersion in oil) in *N*-methylpyrrolidinone (20mL). The adduct was
 deprotected with HCl (4M in dioxane) to afford the titled adduct (0.2g) as a white solid.
 m/e 464 (M+H⁺, 100%)

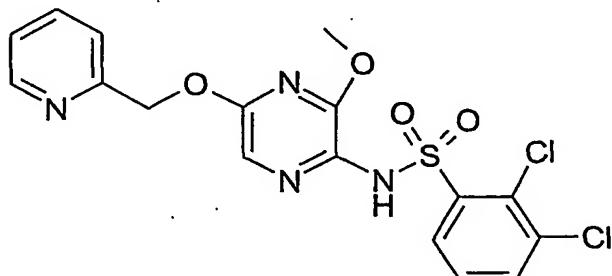
20 ¹H NMR (D6-DMSO) δ 11.24 (1H, br s), 9.46 (1H, br s), 8.99 (1H, br s), 8.01 (1H, d),
 7.96 (1H, d), 7.59 (1H, m), 4.61 (1H, dd), 4.46 (1H, dd), 3.95 (1H, br s), 3.85 (3H, s), 3.19
 (2H, br s), 2.16-2.07 (1H, br s), 2.03-1.94 (1H, br s), 1.92-1.85 (1H, br s), 1.81-1.72 (1H,
 br s).

MP 200-204°C

25

Example 193

2,3-Dichloro-N-[3-methoxy-5-(2-pyridinylmethoxy)-2-pyrazinyl]benzenesulphonamide Hydrochloride



Procedure as for Example 115 using *N*-(5-chloro-3-methoxy-2-pyrazinyl)-2,3-dichloro-*N*-({2-[(trimethylsilyl)oxy]ethoxy}methyl)benzenesulphonamide (Example 115a) (0.5 g), pyridine-3-methanol (0.11 g) and sodium hydride (0.05g of a 60% dispersion in oil) in *N*-methylpyrrolidinone (5mL). Yield 0.23g.

5 m/e 438 (M-1⁺, 100%)

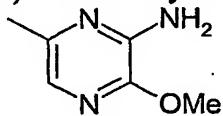
¹H NMR (D6-DMSO) δ 10.9 (1H, br s), 8.7 (1H, br s), 8.12 (1H, t), 7.99-7.92 (2H, m), 7.74 (1H, d), 7.61 (1H, s), 7.63-7.53 (2H, m), 5.54 (2H, s), 3.73 (3H, s).

MP 180-183°C.

10 **Example 194**

2,3-Dichloro-*N*-(3-methoxy-6-methyl-2-pyrazinyl)benzenesulphonamide

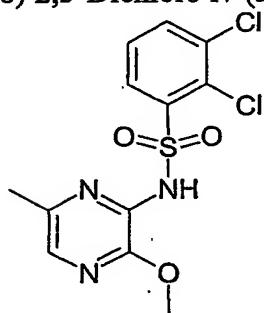
a) 3-Methoxy-6-methyl-2-pyrazinamine



15 To a solution of 5-bromo-3-methoxy-6-methyl-2-pyrazinamine (Example 118c) (0.8g) and ammonium formate (0.4g) in methanol (20mL) was added palladium on carbon (0.2g) and the reaction mixture heated at reflux for 5h. After cooling to room temperature, the reaction mixture was filtered through a plug of celite, and the filtrate evaporated. The residue was partitioned between dichloromethane and water, and the organic phase dried (MgSO₄), filtered and evaporated to give the title compound as a white solid (0.44g).

20 ¹H NMR (D6-DMSO) δ 7.10 (1H, s), 6.15 (2H, br s), 3.83 (3H, s), 2.14 (3H, s)

b) 2,3-Dichloro-*N*-(3-methoxy-6-methyl-2-pyrazinyl)benzenesulphonamide



25 A solution of 3-methoxy-6-methyl-2-pyrazinamine (Example 194a) (0.050g) and 2,3-dichlorobenzenesulphonyl chloride (0.098g) in pyridine (0.3mL) was stirred at room temperature for 18h. Solvent was evaporated to give a residue which was purified by chromatography on silica gel eluting with dichloromethane/ethyl acetate/acetic acid (200:4:1) giving the title compound as a pale orange solid (0.071g).

m/e 348/350 ($M+H^+$, 100%)

1H NMR (D_6 -DMSO) δ 11.44 (1H, br s), 8.14 (1H, dd), 7.92 (1H, dd), 7.65 (1H, br s), 7.61 (1H, t), 3.85 (3H, s), 2.07 (3H, br s).

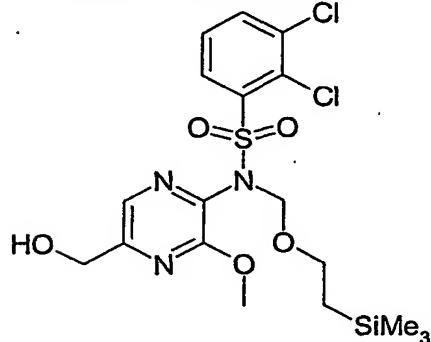
MP 50-60°C

5

Example 195

2,3-Dichloro-*N*-[3-methoxy-5-(1*H*-1,2,4-triazol-1-ylmethyl)-2-pyrazinyl]benzenesulphonamide

a) 2,3-Dichloro-*N*-[5-(hydroxymethyl)-3-methoxy-2-pyrazinyl]-*N*-{[2-(trimethylsilyl)ethoxy]methyl}benzenesulphonamide

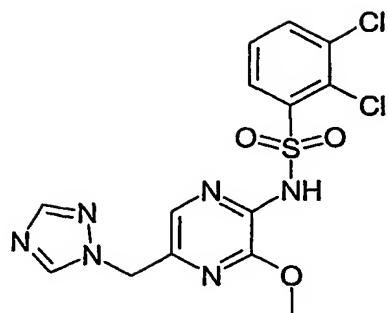


To a suspension of 2,3-dichloro-*N*-[5-(hydroxymethyl)-3-methoxy-2-pyrazinyl]-benzenesulphonamide (1.0g) in dichloromethane (100mL) was added diisopropylethylamine (0.57mL) and 2-(trimethylsilyl)ethoxymethyl chloride (0.58mL).

15 The reaction mixture was stirred at room temperature for 0.5h, then washed with water. The organic phase was dried ($MgSO_4$), filtered and evaporated to give a yellow oil. This was purified by chromatography on silica gel eluting with dichloromethane/ethyl acetate mixtures to give the title compound as a colourless oil (0.8g).

1H NMR ($CDCl_3$) δ 8.04 (1H, s), 7.99 (1H, d), 7.66 (1H, d), 7.28 (1H, t), 5.27 (2H, s), 4.74 (2H, d), 3.90 (3H, s), 3.78 (2H, m), 2.58 (1H, t), 0.85 (2H, m), 0.00 (9H, s).

b) 2,3-Dichloro-*N*-[3-methoxy-5-(1*H*-1,2,4-triazol-1-ylmethyl)-2-pyrazinyl]benzenesulphonamide



To a solution of 2,3-dichloro-N-[5-(hydroxymethyl)-3-methoxy-2-pyrazinyl]-N-[(2-(trimethylsilyl)ethoxy)methyl]benzenesulphonamide (Example 195a) (0.1g) and triethylamine (0.056mL) in dichloromethane (5mL) at 0°C was added methanesulphonyl chloride (0.019mL) and the reaction mixture stirred at 0°C for 1h and room temperature for 1h. The solution was filtered through a plug of silica washing with ethyl acetate and concentrated *in vacuo* to give a colourless oil (0.082g). This was dissolved in *N,N*-dimethylformamide (0.5mL) and 1,2,4-triazole (0.013g) and sodium carbonate (0.026g) added. The reaction mixture was heated at 60°C for 18h, then partitioned between ethyl acetate and saturated aqueous ammonium chloride (5x). The organic phase was dried (MgSO₄), filtered and evaporated. The residue was dissolved in trifluoroacetic acid (2mL) and dichloromethane (2mL). After 20min, removal of solvent *in vacuo* gave a residue which was purified by chromatography on silica gel eluting with ethyl acetate/acetic acid mixtures to give the title compound a pale yellow solid (0.011g).

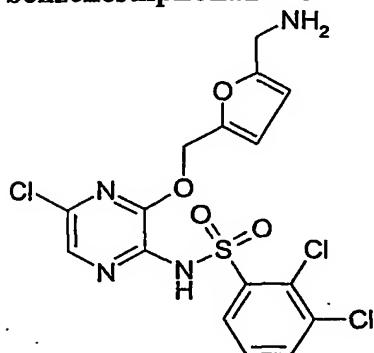
m/e 413/415 (M-H⁻, 100%)

¹H NMR (CDCl₃) δ 8.27 (2H, m), 8.0 (1H, br s), 7.94 (1H, s), 7.68 (1H, d), 7.58 (1H, br s), 7.41 (1H, t), 5.25 (2H, s), 3.97 (3H, s).

MP 95-105°C

20 **Example 196**

N-(3-(5-Aminomethyl-2-furanylmethoxy)-5-chloro-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide



Prepared by the method of Example 31 using (5-aminomethyl-2-furanyl)methanol (0.2g) and 2,3-dichloro-*N*-(3,5-dichloro-2-pyrazinyl)benzenesulphonamide (Example 74) (0.3g). Purified by silica gel chromatography eluting with methanol/dichloromethane mixtures. Yield 0.1g.

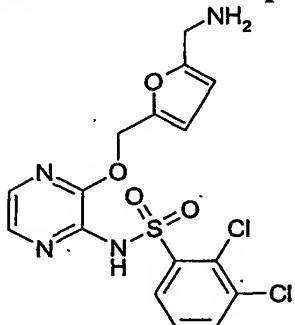
5 m/e 463 ($M+1^+$, 100%)

1 H NMR (D6-DMSO) δ 8.25 (2H, br s), 7.92 (1H, dd), 7.61 (1H, dd), 7.35 (1H, t), 7.27 (1H, s), 6.66 (1H, d), 6.57 (1H, d), 5.19 (2H, s), 4.14 (2H, s)

MP 201-202°C

10 **Example 197**

N-(3-(5-Aminomethyl-2-furanylmethoxy)-2-pyrazinyl)-2,3-dichlorobenzenesulphonamide



Prepared by the method of Example 28 using (5-aminomethyl-2-furanyl)methanol (0.2g)

15 and 2,3-dichloro-*N*-(3-chloro-2-pyrazinyl)benzenesulphonamide (Example 28) (0.3g).

Purified by silica gel chromatography eluting with methanol/dichloromethane mixtures.

Yield 0.2g.

20 m/e 427 ($M-1^+$, 100%)

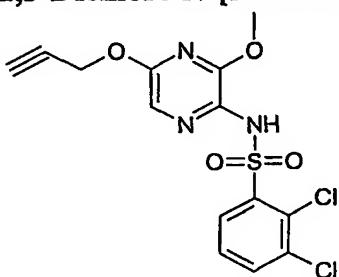
1 H NMR (D6-DMSO) δ 8.40 (2H, br s), 7.96 (1H, dd), 7.60 (1H, dd), 7.35 (1H, t), 7.24

20 (1H, d), 7.15 (1H, d), 6.64 (1H, d), 6.57 (1H, d), 5.20 (2H, s), 4.13 (2H, s)

MP 199-201°C

Example 198

2,3-Dichloro-*N*-(3-methoxy-5-(2-propyn-1-yloxy)-2-pyrazinyl)benzenesulphonamide



Procedure as for Example 115 using 2,3-dichloro-*N*-(5-chloro-3-methoxy-2-pyrazinyl)-*N*-({2-[(trimethylsilyl)oxy]ethoxy}methyl)benzenesulphonamide (Example 115a) (0.25g), propargyl alcohol (0.025mL) and sodium hydride (0.035g of a 60% dispersion in oil) in *N,N*-dimethylformamide (5mL). Yield 0.05g.

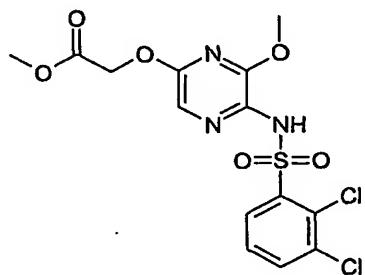
5 m/e 388 ($M+1^+$, 100%)

^1H NMR (D6-DMSO) δ 10.90 (1H, s), 7.98-7.94 (2H, m), 7.55 (1H, t), 7.51 (1H, s), 4.97 (2H, d), 3.85 (3H, s), 3.56 (1H, t)

MP 110-112°C

10 **Example 199**

{[5-(2,3-Dichlorophenylsulfonylamino)-6-methoxy-2-pyrazinyl]oxy}acetic acid, methyl ester



Procedure as for Example 115 using 2,3-dichloro-*N*-(5-chloro-3-methoxy-2-pyrazinyl)-*N*-

15 ({2-[(trimethylsilyl)oxy]ethoxy}methyl)benzenesulphonamide (Example 115a) (0.26g), methyl glycolate (0.075mL) and sodium hydride (0.035g of a 60% dispersion in oil) in *N,N*-dimethylformamide (5mL). Yield 0.1g

m/e 422 ($M+1^+$, 100%)

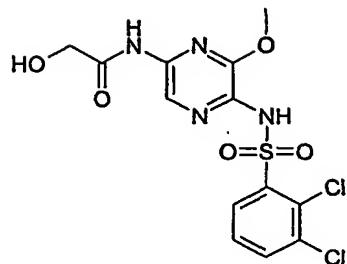
^1H NMR (D6-DMSO) δ 10.89 (1H, s), 7.99-7.92 (2H, m), 7.58-7.53 (2H, m), 4.92 (2H, s),

20 3.75 (3H, s), 3.68 (3H, s).

MP 185-190°C

Example 200

N-[5-(2,3-Dichlorophenylsulphonylamino)-6-methoxy-2-pyrazinyl]-2-hydroxyacetamide



Procedure as for Example 115 using 2,3-dichloro-*N*-(5-chloro-3-methoxy-2-pyrazinyl)-*N*-({2-[(trimethylsilyl)oxy]ethoxy}methyl)benzenesulphonamide (Example 115a) (0.25g),

5 glycolamide (0.066g) and sodium hydride (0.035g of a 60% dispersion in oil) in *N,N*-dimethylformamide (5mL). Yield 0.075g.

m/e 407 (M+1⁺, 100%)

¹H NMR (D6-DMSO) δ 11.23 (1H, br s), 9.77 (1H, s), 8.36 (1H, s), 8.05 (1H, dd), 7.94 (1H, dd), 7.58 (1H, t), 4.04 (2H, s), 3.86 (3H, s).

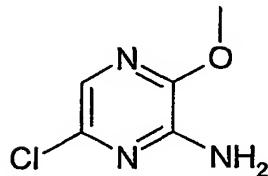
10 MP 153-155°C

Example 201

6-(2,3-Dichlorophenylsulphonylamino)-5-methoxy-2-pyrazinecarboxylic acid, methyl ester

15

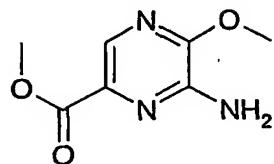
a) 6-chloro-3-methoxy-2-pyrazinamine



A mixture of 5-bromo-6-chloro-3-methoxy-2-pyrazinamine (Example 125a) (0.6g),

20 triethylamine (0.72mL), 10% palladium on carbon (0.05g) and ethyl acetate (50mL) were hydrogenated at 0.5 bar until reaction was complete as judged by hydrogen uptake. The reaction mixture was filtered and washed with water (25mL), dried (MgSO₄), filtered and evaporated to afford the sub-titled compound (0.33g). Used Directly.

25 b) 6-Amino-5-methoxypyrazine-2-carboxylic acid methyl ester

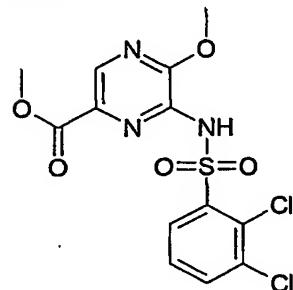


Prepared as for Example 113 using 6-chloro-3-methoxy-2-pyrazinamine (Example 201a) (0.35g) heated at 120°C for 3h. Yield 0.3g.

m/e 184(M+1⁺, 100%)

5

c) 6-(2,3-Dichlorophenylsulphonylamino)-5-methoxy-2-pyrazinecarboxylic acid, methyl ester



Prepared by the method of Example 1 (reaction performed at room temperature) using 6-amino-5-methoxypyrazine-2-carboxylic acid methyl ester (Example 201b) (0.3g) and 2,3-dichlorobenzenesulphonyl chloride (0.4g). Yield 0.15g.

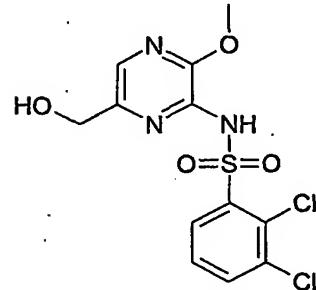
m/e 392 (M+1⁺, 100%)

¹H NMR (D6-DMSO) δ 8.39 (1H, s), 8.25 (1H, dd), 7.93 (1H, dd), 7.65 (1H, t), 3.99 (3H, s), 3.77 (3H, s)

15 MP 90-92°C

Example 202

2,3-Dichloro-N-[6-(hydroxymethyl)-3-methoxy-2-pyrazinyl]benzenesulphonamide



20 Prepared as for example 120 using 6-(2,3-dichlorophenylsulphonylamino)-5-methoxy-2-pyrazinecarboxylic acid, methyl ester (Example 201) (0.12g). Yield 0.03g.

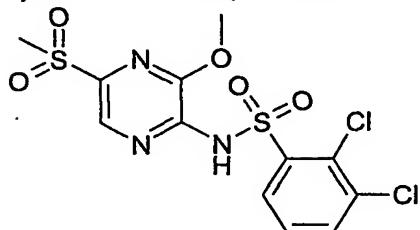
m/e 364 (M+1⁺, 100%)

¹H NMR (D6-DMSO) δ 11.5 (1H, br s), 8.13 (1H, dd), 7.92 (1H, dd), 7.77 (1H, br s), 7.59 (1H, t), 5.25 (1H, br s), 4.19 (2H, s), 3.87 (3H, s).

MP 153-155°C

5 Example 203

2,3-Dichloro-N-(5-methanesulphonyl-3-methoxy-2-pyrazinyl)benzenesulphonamide



Oxone (potassium peroxyomonosulphate) (0.6g) was added to 2,3-dichloro-N-(3-methoxy-5-methylsulphonyl-2-pyrazinyl)benzenesulphonamide (Example 80) (0.3g) in methanol (40mL) and water (10mL) and the mixture heated at 50°C for 4h. After cooling, the mixture was filtered and evaporated. Purified by silica gel chromatography eluting with ethyl acetate/iso-hexane mixtures containing 1% acetic acid to give the title compound.

Yield 0.2g.

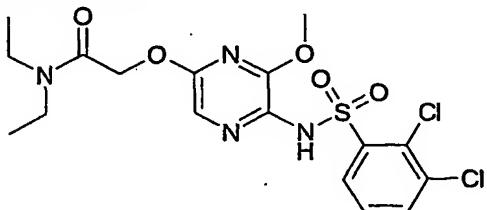
m/e 411 (M-1⁺, 100%)

15 ¹H NMR (CDCl₃) δ 8.33 (1H, s), 8.30 (1H, s), 8.23 (1H, br s), 7.72 (1H, dd), 7.47 (1H, t), 4.14 (3H, s), 3.11 (3H, s)

MP 237-238°C

Example 204

20 2-[5-(2,3-Dichlorobzenesulphonylamino)-6-methoxy-2-pyrazinyl]oxy]-N,N-diethylacetamide



Prepared as for Example 115b using N-(5-bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-N-[{2-(trimethylsilyl)ethoxy}methyl]benzenesulphonamide (Example 55a) (0.35g) and 25 N,N-diethyl-2-hydroxyacetamide (0.13g). Yield 0.2g

m/e 463 (M+1⁺, 100%)

¹H NMR (CDCl₃) δ 8.22 (1H, dd), 7.68 (1H, dd), 7.52 (1H, s), 7.46 (1H, s), 7.37 (1H, t), 4.88 (2H, s), 3.92 (3H, s), 3.38 (2H, q), 3.30 (2H, q), 1.20 (3H, t), 1.11 (3H, t)

MP 117-118°C

Example 205

2,3-Dichloro-N-{5-[2-(dimethylamino)ethylsulphanyl]-3-methoxy-2-pyrazinyl}benzenesulphonamide



Prepared as for Example 101b using *N*-(5-bromo-3-methoxy-2-pyrazinyl)-2,3-dichloro-*N*{[2-(trimethylsilyl)ethoxy]methyl}benzenesulphonamide (Example 55a) (0.3g) and 2-(dimethylamino)ethanethiol hydrochloride (0.2g). Yield 0.25g.

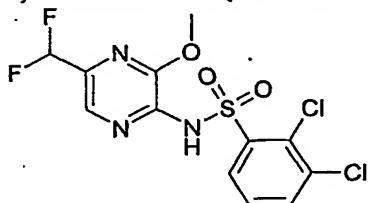
m/e 435(M-1⁺, 100%)

¹H NMR (D6-DMSO) δ 8.05 (1H, dd), 7.95 (1H, dd), 7.71 (1H, s), 7.58 (1H, t), 3.98 (3H, s), 3.47 (2H, m), 3.28 (2H, m), 2.77 (6H, s)

MP 117-118°C

Example 206

2,3-Dichloro-N-(5-difluoromethyl-3-methoxy-2-pyrazinyl)benzenesulphonamide



(Diethylamino)sulphur trifluoride (DAST) (0.15g) and 2,3-dichloro-*N*-(5-formyl-3-methoxy-2-pyrazinyl)benzenesulphonamide (Example 186a) (0.3g) in dichloromethane (20mL) was stirred at room temperature for 4h and then evaporated. Purified by silica gel chromatography eluting with ethyl acetate/iso-hexane mixtures to give the title compound. Yield 0.06g.

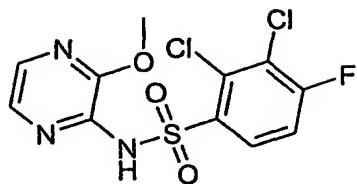
m/e 382(M-1⁺, 100%)

¹H NMR (D6-DMSO) δ 8.14 (1H, dd), 7.96 (1H, dd), 7.84 (1H, s), 7.60 (1H, t), 6.80 (1H, t), 3.95 (3H, s)

MP 117-118°C

Example 207

2,3-Dichloro-4-fluoro-N-(3-methoxy-2-pyrazinyl)benzenesulphonamide



Sodium hydride (0.4g of a 60% dispersion in oil) was added to a solution of 3-methoxy-2-pyrazinamine (0.25g) in *N*-methylpyrrolidinone (10mL). After 0.5h, 2,3-dichloro-4-fluorobenzenesulphonyl chloride (Example 185a) (0.63g) was added. After 16h at room temperature the reaction mixture was quenched with 2M aqueous HCl, extracted with ethyl acetate, dried (MgSO_4) and evaporated. Purification was by silica gel chromatography eluting with ethyl acetate/*iso*-hexane mixtures. Yield 0.16g.

5 m/e 350/352 ($\text{M}+1^+$, 100%)

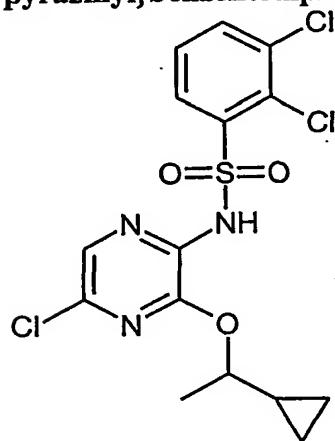
10 ^1H NMR (D_6 -DMSO) δ 8.16 (1H, dd), 7.78 (1H, br s), 7.68 (1H, t), 7.62 (1H, br s), 3.9

15 (3H, s)

MP 192-194 °C

Example 208

2,3-Dichloro-N-{5-chloro-3-[1-(cyclopropyl)ethoxy]-2-pyrazinyl}benzenesulphonamide



15 Prepared by the method of Example 31b using 1-(cyclopropyl)ethanol (0.1g) and 2,3-dichloro-N-(3,5-dichloro-2-pyrazinyl)benzenesulphonamide (Example 74) (0.1g). Yield 0.04g.

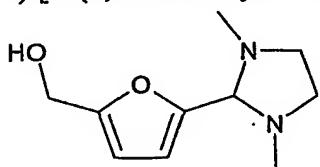
20 m/e 422 ($\text{M}+1^+$, 100%)

^1H NMR (D_6 -DMSO) δ 11.70-11.50 (1H, br s), 8.07 (1H, dd), 7.94 (1H, dd), 7.77 (1H, s), 7.59 (1H, t), 4.60-4.50 (1H, m), 1.33 (3H, d), 1.1-1.0 (1H, m), 0.6-0.3 (4H, m)

MP 161-162 °C

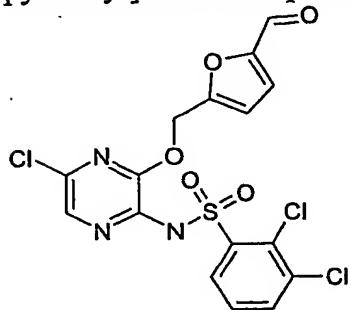
Example 209**2,3-Dichloro-N-[5-chloro-3-(5-formyl-2-furanylmethoxy)-2-pyrazinyl]benzenesulphonamide**

5 a) [5-(1,3-Dimethyl-2-imidazolidinyl)-2-furanyl]methanol



5-hydroxymethylfuran-2-carbaldehyde (5.0g) and *N,N'*-dimethylethane-1,2-diamine (3.8g) in toluene (100mL) was heated under reflux using a Dean and Stark apparatus. After 12h, the toluene was evaporated to give an oil. Yield 8.3g. Used directly.

10 b) 2,3-Dichloro-N-[5-chloro-3-(5-formyl-2-furanylmethoxy)-2-pyrazinyl]benzenesulphonamide

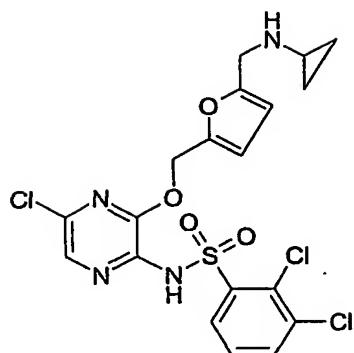


15 Prepared by the method of Example 31b (reaction heated at 60°C for 4h) using [5-(1,3-dimethyl-2-imidazolidinyl)-2-furanyl]methanol (2.3g) and 2,3-dichloro-N-(3,5-dichloro-2-pyrazinyl)benzenesulphonamide (Example 74) (3.0g). The reaction was quenched with 2M hydrochloric acid and left for 16h. The solid product was collected. Purified by silica gel chromatography eluting with ethyl acetate/iso-hexane mixtures to give the title compound. Yield 2.5g.

20 m/e 460 (M+1⁺, 100%)

¹H NMR (D6-DMSO) δ 9.64 (1H, s), 8.06 (1H, dd), 7.94 (1H, dd), 7.87 (1H, s), 7.57 (2H, d+t), 6.93 (1H, d), 5.47 (2H, d)

Example 210**2,3-Dichloro-N-[5-chloro-3-(5-cyclopropylaminomethyl-2-furanylmethoxy)-2-pyrazinyl]benzenesulphonamide**



Prepared by the method of Example 107b using 2,3-dichloro-N-[5-chloro-3-(5-formyl-2-furanylmethoxy)-2-pyrazinyl]benzenesulphonamide (Example 209) (0.3g) and cyclopropylamine (0.1g). Yield 0.1g.

5 m/e 503 (M-1⁺, 100%)

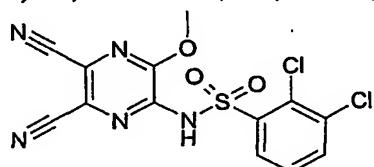
¹H NMR (D6-DMSO) δ 7.93 (1H, dd), 7.63 (1H, dd), 7.36 (1H, t), 7.30 (1H, s), 6.66 (1H, d), 6.63 (1H, d), 5.21 (2H, s), 4.34 (2H, s), 2.71 (1H, m), 0.76 (4H, m)

MP 175-176°C

10 **Example 211**

N-[5,6-*bis*-(Hydroxymethyl)-3-methoxy-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide

a) 2,3-Dichloro-*N*-(5,6-dicyano-3-methoxy-2-pyrazinyl)benzenesulphonamide

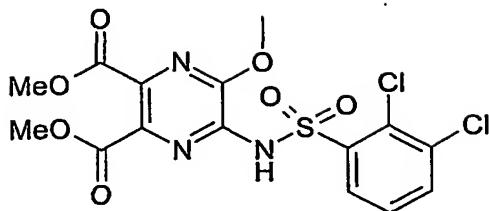


15

Prepared by the method outlined in Example 1 using 5-amino-6-chloro-2,3-dicyanopyrazine (1.8g) and 2,3-dichlorobenzenesulfonyl chloride (2.7g). The adduct was reacted by the method outlined in example 31b using sodium methoxide to afford the substituted compound that was used directly.

20 m/e 382, 383 (M-1⁺, 100%)

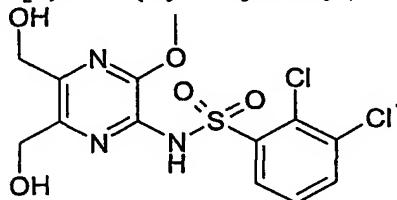
b) 5-{{(2,3-Dichlorophenyl)sulphonyl]amino}-6-methoxypyrazine-2,3-dicarboxylic acid, dimethyl ester



The crude product from above (Example 211a) was dissolved in 10% aqueous sodium hydroxide solution and heated under reflux for 10 hours. The reaction mixture was cooled, concentrated and the residue was treated with thionyl chloride (30mL) and refluxed for 1 hour, cooled and concentrated, azeotroping with dry toluene. The resulting residue was dissolved in methanol (30mL) and allowed to stand for 10 hours and concentrated to afford the sub-titled compound that was used directly.

m/e 448, 450 (M-1⁺, 100%)

c) N-[5,6-bis-(Hydroxymethyl)-3-methoxy-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide



To a solution of 5-{{[(2,3-dichlorophenyl)sulphonyl]amino}-6-methoxypyrazine-2,3-dicarboxylic acid, dimethyl ester (Example 211b, 0.5g) dissolved in anhydrous tetrahydrofuran (20 mL) at 0°C was added a solution of lithium triethylborohydride (Super hydride®) (5.55 mL of a 1M solution in tetrahydrofuran) and the resulting solution was stirred for 1 hour. The reaction was quenched by the addition of 1N hydrochloric acid (10 mL) and extracted into ethyl acetate (2x20mL). The combined extracts were dried (MgSO₄), filtered and concentrated to afford an oil that was purified by chromatography on silica gel eluting with ethyl acetate/dichloromethane mixtures to afford the titled compound (0.201 g) as a foam.

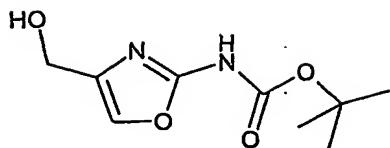
m/e 392, 394 (M-1⁺, 100%)

¹H NMR (CDCl₃) δ 8.30 (1H, d); 7.91 (1H, br s), 7.71 (1H, d), 7.46 (1H, t), 4.59 (2H, s), 4.50 (2H, s), 4.0 (3H, s)

Example 212

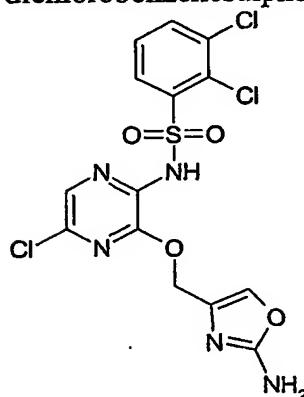
N-[3-[(2-amino-4-oxazolyl)methoxy]-5-chloro-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide

a) (4-Hydroxymethyl-2-oxazolyl)carbamic acid *tert*-butyl ester



Prepared by the method of Example 120 using 2-{bis[(1,1-dimethylethoxy)carbonyl]amino}-4-oxazolcarboxylic acid, ethyl ester (0.65g) and sodium triethylborohydride (5.5mL of a 1M solution in tetrahydrofuran). Yield 0.24g. Used directly.

b) *N*-[3-[(2-amino-4-oxazolyl)methoxy]-5-chloro-2-pyrazinyl]-2,3-dichlorobenzenesulphonamide



Prepared by the method of Example 112 using (4-hydroxymethyl-2-oxazolyl)carbamic acid *tert*-butyl ester (Example 212a) (0.12g) and 2,3-dichloro-*N*-(3,5-dichloro-2-pyrazinyl)benzenesulphonamide (Example 74) (0.21g). Purification was by silica gel chromatography eluting with ethyl acetate/*iso*-hexane mixtures to give the title compound with the BOC (*tert*-butyl carbonyl) attached (0.11g). This compound was dissolved in trifluoroacetic acid (1.5mL) and dichloromethane (1.5mL). After 2h, the solution was evaporated. Purification was by silica gel chromatography eluting with ethyl acetate/*iso*-hexane mixtures to give the title compound. Yield 0.08g.

m/e 450 (M+1⁺, 100%)

¹H NMR (D6-DMSO) δ 8.04 (1H, dd), 7.91 (1H, dd), 7.80 (1H, s), 7.55 (1H, t), 7.49 (1H, s), 6.71 (2H, br s), 5.10 (2H, s).

MP 137°C

Pharmacological Analysis

FMAT Whole cell binding assay

5

Cells

CHO-K1 cells stably expressing the human recombinant CCR4 receptor (Euroscreen; Brussels, Belgium) were cultured in NUT MIX.F_12(HAM) medium with glutamax-1, 10 containing 10% (v/v) foetal bovine serum and 400 μ g ml⁻¹ geneticin.

Cells were harvested at approximately 70% confluence by treatment with a cell dissociation buffer, and seeded at 5x10³ cells/100 μ l culture medium into wells of a black Costar clear-bottomed 96-well microtitre plates. Plates were incubated overnight at 37°C 15 in 5% CO₂ and used the following day.

ASSAY

Before use, the cell plates were washed twice with 100 μ l Hanks balanced salt solution (HBSS). To each well was then added 65 μ l of HBSS, 10 μ L of 10% DMSO in HBSS ± 20 test compound and then 25 μ L of 2.8 nM FB-MDC (Applied Biosystems). This fluorescent probe was prepared from a 10 μ M stock in 0.08% (v/v) TFA/16% (v/v) acetonitrile, diluted into HBSS.

25 After two hours incubation in the dark at room temperature, the plates were analysed in an FMAT8100 reader (Applied Biosystems) to measure fluorescence that was associated with binding of FB-MDC to the cells. Compound activity was determined as an pIC₅₀ [log(concentration of compound that results in 50% inhibition)], comparing fluorescence in control and background wells.

30

Typical Data

Fluorescence (ctrl) = 1200

Fluorescence (bkg) = 0

35

The compounds of the examples all have a pIC₅₀ of greater than 5.0.

Data for specific compounds is given below.

		Mean
	Example 112	pIC ₅₀ 9.5
5	Example 119	pIC ₅₀ 7.2
	Example 186	pIC ₅₀ 6.2

10

15

20

25

30

35